Volume XXI Number 8

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

AUGUST
1960

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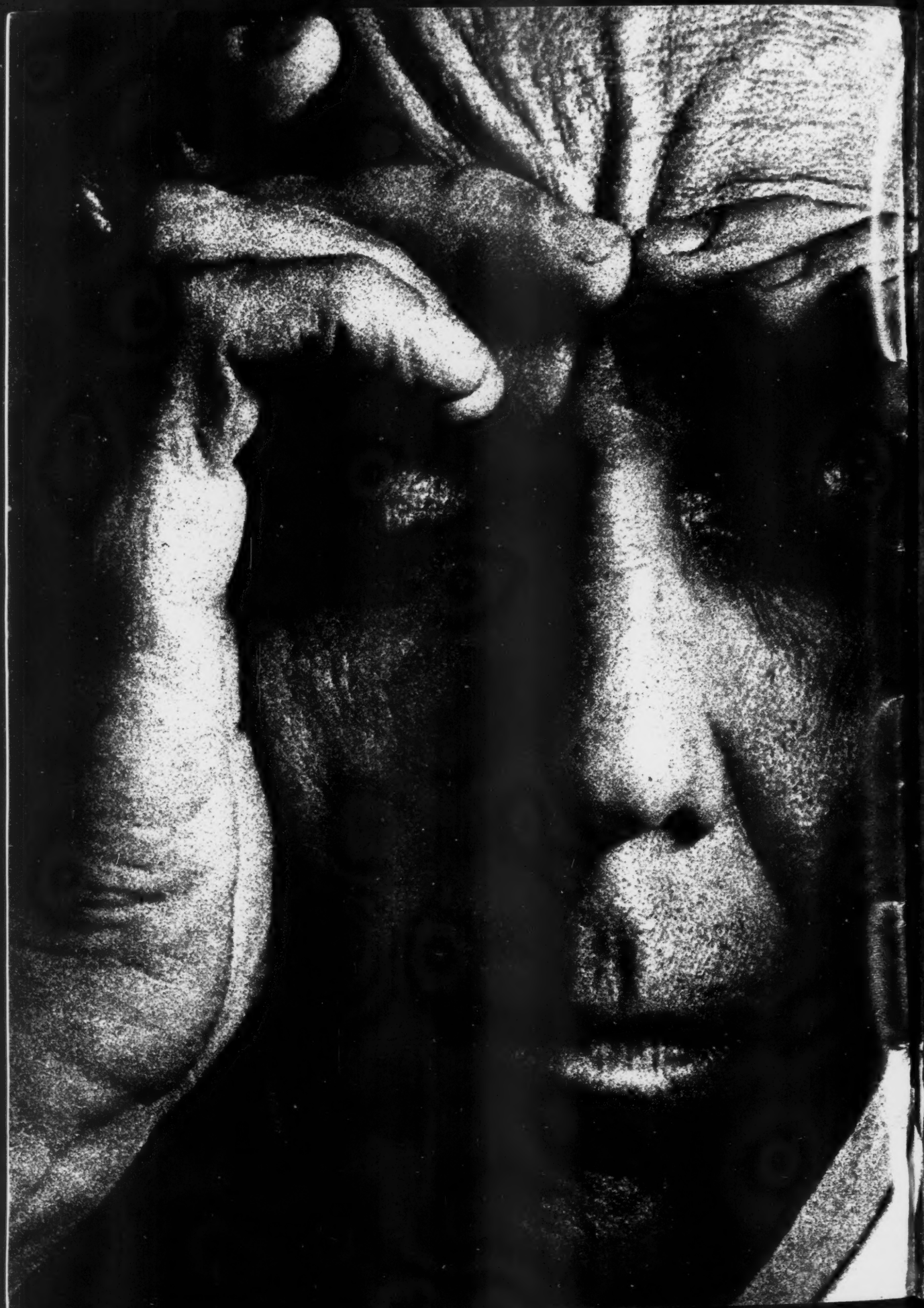

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1. Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **4.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **5.** Landman, M. E. (50 patients): Choosing the right drug for the patient. Submitted for publication, 1960. **6.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Kanefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **7.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **8.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **9.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **10.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination (Deprol). Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **11.** Splitter, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

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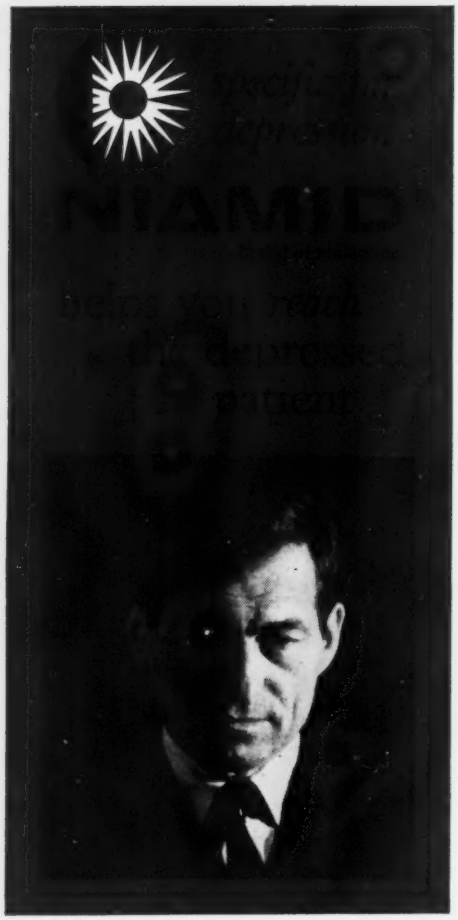

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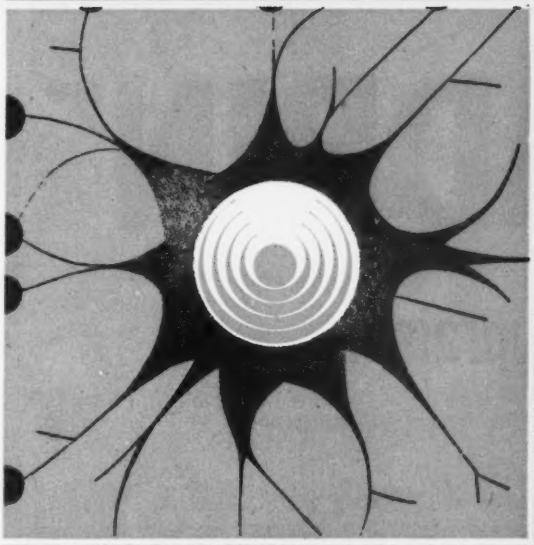

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1. Konchegul, L.: M. Ann. D. of C. **27**:405 (Aug.) 1958.
2. Kruse, W.: Dis. Nerv. System **21**:79 (Feb.) 1960.
3. Zier, A. and Doshay, L. J.: Neurology 7:485 (July) 1957.
4. Lerner, P. F.: J. Nerv. & Ment. Dis. **123**:79 (Jan.) 1956.

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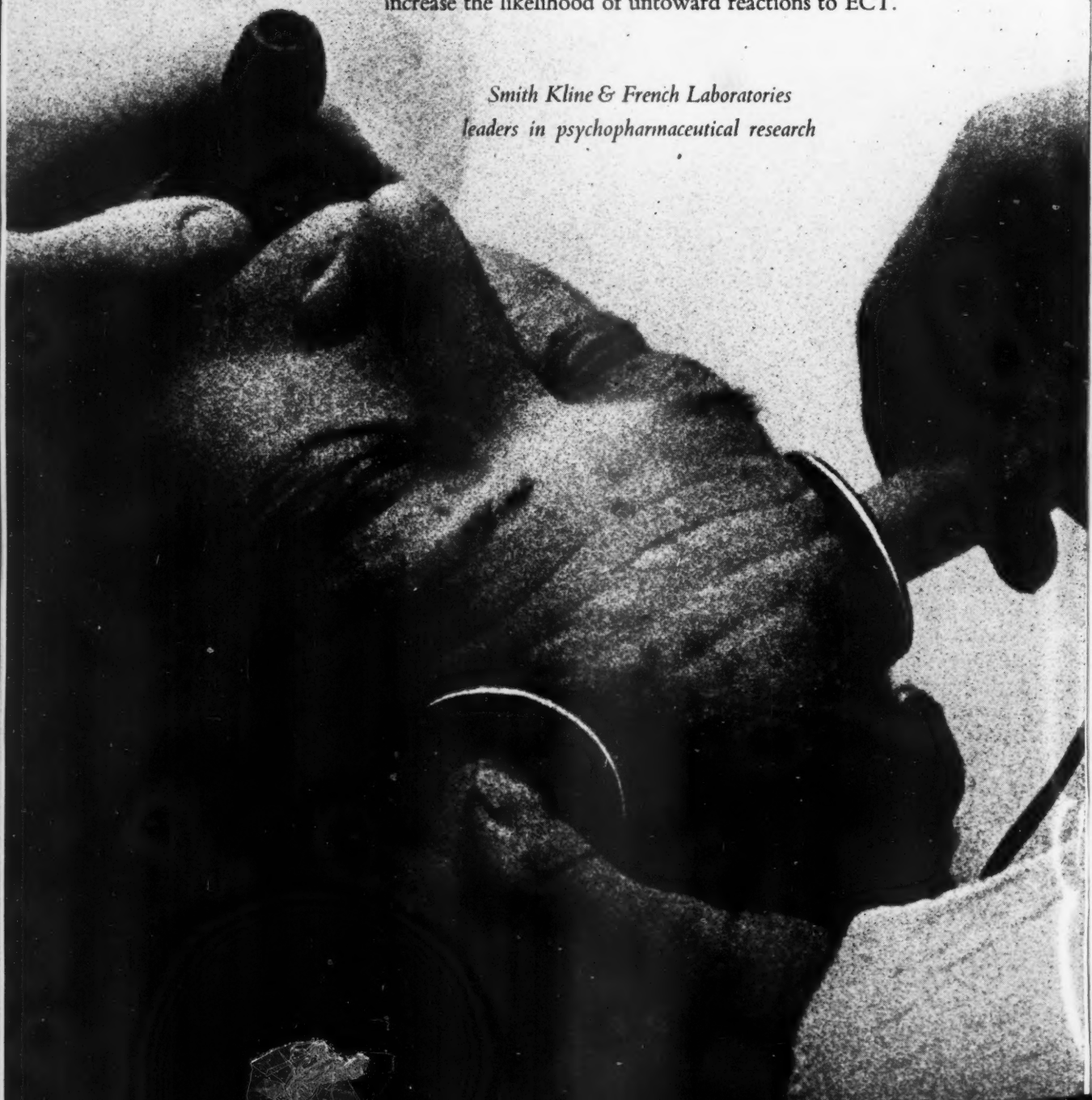

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Creativity, Consciousness and Revelation

NATHANIEL S. LEHRMAN

This paper will attempt to define the relationship between creativity and consciousness, taking into account recent neurophysiological, psychological and psychoanalytic research. Revelation will also be considered, as a special case of creativity.

What Is Creativity?

Bronowski has defined creativity as "the finding of a new unity in the variety of nature."[1] "The creative scientist," he writes, finds "likeness between things which were not thought alike before." The creative artist also illustrates, through his particular medium, a new relationship between aspects of reality. The new relationship in reality between mass and energy which Einstein discovered is a creative product similar to the new, fragrant psychological relationship between a rose and beloved Romeo which Shakespeare created in his line, "A rose by any other name would smell as sweet." The latter has, of course, many other psychological overtones of similar creative quality.

Creativity is derived primarily from the process of inductive reasoning, in which one generalization is made from several specific data. In this paper, we are primarily concerned with the neurophysiological processes whereby these new, unifying generalizations are created.

What Is Consciousness?

In his review of "The Physiological Basis of Consciousness"[2] Sir Russell Brain lists at least six different kinds of answers to this question. For our purpose, "consciousness," in animals or in men, is best defined as the subjective aspect of the process of making, or preparing to make, motor choices. In humans, "motor choices" include spoken responses.

In all species, "consciousness" is connected with emotionality and the basic pleasure-approach and pain-withdrawal drives. Even in humans, as Sherrington wrote, "every cognition has, potentially at least, an emotive value."[3] In addition, human consciousness has an extra dimension beyond the "consciousness" of other species because of its inextricable connection with verbalization and with the speech centers.

Motor choices are made as the result of the interaction within the central nervous system of contemporaneous stimuli, inborn reflex patterns, and memory traces of past experiences. Eccles has suggested the nature of the neurophysiological processes whose interaction and integration determine the final motor response.

"Each of the sense organs reports on its own lines to . . . specific regions in the cortex. . . . We may speculate that a wave-front (of discharging cells) initiated by the arrival of a sensory signal in the cortex preserves the specificity of that signal as it propagates through the neuronal network. We may further assume that the interaction of wave-fronts originating at different sites in the cortex effects the integration and synthesis of the information relayed from different sensory receptors."

"For example," he continues, "a wave-front initiated by the sensation of pressure on a certain area of skin, interacting with wave-fronts signaling muscle sensation and cold, integrates in a assembled wave form characteristic of a smooth, cold object of a certain shape and mass—perhaps a stone."

Thus, in humans, one verbal symbolic stimulus such as the word "stone" can represent the entire integrated wave form characteristic of the stone. But how is it remembered?

Here, too, Eccles offers an answer.

"Theory and even some experimental evidence favor the hypothesis that the initial activation of

the synapses in a network brings about a lasting improvement in the efficacy of these junctions. As yet, no one knows how. . . . For the present, it is sufficient to consider the increased synaptic function as giving a 'congealed' neuronal pattern or 'engram' ready to be replayed by an appropriate input."

Hence the word "stone" can not only represent an integrated complex of sensations, or any part of it, but it can evoke them as well. One symbol can thus both represent and evoke many sensory data.

Since the brain can simultaneously handle only a limited number of stimuli effectively, the more each symbolic stimulus represents, the greater the number of sensory data which can be meaningfully handled, and consequently the greater the efficiency of making motor choices. The social creation and use of ever more inclusive symbols thus makes possible the inclusion of more experiential data in this process of integrating stimuli, reflexes and memories in the determination of motor responses.

The interaction of symbols in creative thinking is presumably similar to, although far more complicated than, the interaction of sensations (including the verbal-auditory) to form the symbol-concept "stone." Each symbol in creative thinking evokes far more complicated engrams than do simple sensations. When several symbols interact, we can thus see how the final engram product will be a synthesis of all that is represented by all the symbols.

Human Consciousness and the Speech Centers

Human consciousness is the *subjective awareness* of the neuro-physiological processes which make choices. But we are aware or conscious of only a small percentage of these processes at any given moment. Which few of the many simultaneous engrammatic interactions are we aware of?

We are most aware, or most conscious, of those particular central nervous system processes which can be most easily defined in verbal terms. The stream of consciousness is indeed the stream of those engrams which can be easily verbalized, wandering or meandering though this stream may be.

Hence we can offer the hypothesis that human consciousness is the subjective reflection of those neurophysiological engrammatic circuits which, at a particular moment, include cells within the conceptual speech centers of the brain. These areas, located primarily in the posterior left temporo-parietal area, mediate integrated conceptualization, as Penfield has shown.[5] In the engrammatic circuits producing actual speech, cells in these temporo-parietal centers apparently immediately precede the cells in the Broca area, which integrate the specific motor activities of mouth and larynx required for vocalization and articulated speech.

"Man alone," writes Penfield,[5] "has an inborn control mechanism for vocalization in his cerebral cortex. . . . Without the help of man's vocalization projection to the newer cortex, it is quite possible that vocalization could not be used in the complicated patterns which he employs for human speech. . . .

"The neurological structures required for another and much more important mechanism are probably missing, too, in the sub-human brain. That is the mechanism employed by man for ideational speech. There is a very large increase in the extent of the temporo-parietal cortex that becomes obvious in passing from anthropoid ape to man. It seems likely that the posterior speech area of the human cortex constitutes a new appearance . . . (which has) taken over this zone as the major ideational speech structure."

The Mechanism of the Conceptual Speech Center, as Determined from Studies of Patients with Brain Damage

Teuber's[6] studies of men who suffered penetrating battle injuries of the brain help us to understand better the disproportionate importance in human ideation, i.e., intelligence, of the conceptual speech center in the left temporo-parietal area. His work shows that damage in this area is apparently far more destructive to intellectual functioning than equicellular damage anywhere else in the cortex.

He studied the performance of these brain-injured men on standard intelligence tests, and on other tests which he devised, by comparing their performance with that of a group of soldiers who had suffered only peripheral nerve injuries. In addition, he com-

pared all the Army intelligence test (AGCT) scores post-injury with those obtained at the time of entry into military service.

Contrary to the usual idea that intelligence test scores are relatively fixed, he found that 48 of his 50 controls

"markedly increased their (AGCT) score; on the average, they . . . gained 13 points, even though ten years . . . intervened between the first and second testing session. . . . Much less expected, however," he continues, "was the fact that among the brain-injured, nearly two-thirds improved their scores, many as much as the controls."

When the test results were analyzed on the basis of the location of the wound of entrance, the only group which showed a mean loss in AGCT score post-injury was that group with entrance wounds in the left temporo-parietal area; all the other brain-injured groups showed a post-traumatic increase in their AGCT scores.

"These results," Teuber states, "can be interpreted in two ways: if one accepts scores on a routine psychometric test, such as the AGCT, at their face value, one would be inclined to conclude that losses in test intelligence are rare or absent unless the injury encroaches upon the left parieto-temporal region. The second and more parsimonious interpretation would emphasize the negative findings first, namely that the AGCT seems insensitive to many of the actual changes that might occur after brain injury unless these changes include some subtle but significant loss of verbal skills. This second interpretation would then stress that a paper and pencil test so intimately tied to language functions as the AGCT would be expected to bring out traces of language trouble even in those patients with left hemisphere lesions who appear to be without aphasia on clinical interview."

Another interpretation might be that the beneficial effects upon intelligence of ten years of living seem greater than the harmful effects of brain injury to all patients, except those suffering from damage to the conceptual speech areas, the left temporo-parietal area. This part of the brain therefore seems particularly necessary for the capacity to improve intellectual functioning, or at least those intellectual functions tested by AGCT.

The Relationship Between Speech and Thought

The relationship between speech and thought has been the subject of very penetrating Russian studies,[7,8] which can perhaps help us better to understand Teuber's findings. We have seen how conceptualization, the process of creating new symbols to represent new ideas, is derived from the processes involved in the production of ideational speech. As has been described above, conscious explicit conceptualization apparently involves passage of engrams through the left temporo-parietal conceptual speech area. But, as Beyn[7] points out, "speech is not merely an external expression of thought (or its 'garments'); 'thought is not only expressed by speech but also accomplished by it'" (p. 235). "Acts of abstraction (are) in their genesis speech acts" (p. 241).

But after a new concept has entered our consciousness and thus produced engrammatic traces within the brain, it can continue to affect mental and behavioral functioning even if it is never spoken again. Conceptual thinking can continue to occur even when the neurological centers of motor speech are impaired. Beyn's studies "help to corroborate the highly important proposition that acts of abstraction, which in their genesis are speech acts, subsequently prove to be relatively independent, and do not require any constant reinforcement by vocal speech" (p. 241).

Damage to the conceptual speech area, however, interferes with abstraction and conceptualization to a much greater extent than equicellular damage elsewhere, as Teuber has shown. Although the abstracting process can continue in large measure in adults (but not in children) even after damage to this area, there is impairment of certain intellectual processes "by the instability of (the patient's) means of verbal thought" (p. 240).

The abstraction process can apparently continue to some extent in adults even after damage to the conceptual speech center, as Luria[8] has demonstrated. From our psychological knowledge, we can now offer a hypothesis as to how this process occurs.

In normal people with intact brains, an act of abstraction or of problem-solving does not usually continue to an explicitly verbalized end, either voiced or silent. When the

solution is not explicitly verbalized, we are aware only of a "feeling" concerning the situation or problem, even though we may in actuality be acting upon it. As will be described below, this "feeling" represents a synthesis of many concepts and experiences interacting outside our explicit conscious awareness.

Often these "feelings" can substitute for words as a mechanism for determining responses to present situations in terms of past experience. These "feeling"-determined responses can include abstractional responses, which in some cases—e.g., simple arithmetic—can be carried out without explicit consciousness during the process. Hence we can see that abstractional or conceptual responses to present situations based on past experience can perhaps still continue to some extent via "feeling," even when explicit consciousness is impaired, as in sensory aphasia.

But although "feelings" can partly substitute for words as a mechanism for interpreting the present in terms of the past, they cannot do so completely. Hence "feelings" can be seen as a supplement to, but not as a complete substitute for, explicit, verbalizable consciousness.

In addition, damage to the conceptual speech center seems to have a more harmful effect on the ability to conceptualize *de novo*, to assimilate and integrate new, simultaneous stimuli, than it does on the ability to determine present responses primarily in terms of past experience.

Luria's[8] studies of brain injured Soviet soldiers shed further light on the way the conceptual speech center apparently operates, and why, when this area is damaged, new learning is apparently impaired more than are responses based on previous abstractions.

"Patients with disorders of the postero-parietal and parieto-occipital sections of the dominant left hemisphere," he writes, "show characteristic disabilities; although still able to understand everyday speech, they are incapable of understanding the meaning of complicated logico-grammatical combinations, which express certain abstract relationships . . . (They) show considerable difficulty in operating with spatial relations of objects, etc." (p. 21).

Luria's findings are similar to Teuber's.[6] After obtaining the results described above on standard intelligence tests, Teuber tried to gauge intellectual functioning, separated from its "verbal" elements, by measuring his subjects' performance on a spatial orientation test. Here "men with parietal injuries (right or left) as a group showed significant defect in performance, while men with lesions elsewhere in the brain showed little or no defect as compared with . . . controls."

Parieto-Occipital Mediation of "Simultaneous Synthesis"

Luria's paper explains his own and Teuber's findings.

"A breakdown of simultaneous synthesis," Luria suggests (p. 24), "can quite justifiably be regarded as the physiological basis of functional disorders occurring in lesions of the parieto-occipital areas of the brain. However, if the lesion goes beyond the limits of the parieto-occipital areas . . . and reaches the border of the speech area, it may produce disorders which go far beyond the limits of the visual realm. They inevitably lead to a breakdown of the more complicated mnemic operations, connected with abstraction of one signal and the synthesis of a series of elements in accordance with this abstracted signal. They also lead inevitably to a situation where operations which use a definite complex code (e.g., ordinary intellectual language—NSL) and which are linked by means of this code with the intellectual act become impossible."

"Psychological) constructions," he continues (p. 26), "which are very complex in form and came into being relatively late are very vulnerable, and inevitably disintegrate when the basic condition indispensable for their understanding is unattainable as a result of the breakdown of complex 'simultaneous synthesis' and of the ability to combine isolated elements into a single analytic 'unit.'"

In other words, the process of simultaneous synthesis, which we have defined previously as an essential part of creativity, is apparently particularly damaged by parieto-occipital lesions. When the damage involves the adjacent sensory speech area, i.e., the left temporo-parietal area, *verbal* simultaneous synthesis becomes impaired, and intellection and creativity suffer most. This is the condition called "semantic aphasia" by

Head; "breakdowns in the complicated system of linguistic constructions," Luria continues (p. 27)

> "caused by affections of the parieto-occipital systems of the brain . . . lead directly to the disintegration of simultaneous synthesis and to the breakdown in the act of 'combining isolated details into a single whole' which Head so rightly pointed out in his time."

The Emergence of the Common Wave Form

It was pointed out above how cortical engrams evoked by different simultaneous sensory stimuli become integrated into one assembled characteristic wave form or engram—of a stone, for example. This emergence of a common neuronal wave form from temporally associated but previously unintegrated stimuli is the neurophysiological foundation of the associative-learning process and of the creative process as well.

The emergence of the new wave form occurs in infra-human species also. There, however, it leads relatively directly to the motor response. In humans, while the resultant common neuronal wave form also produces motor response, there is, apparently, an intermediate step, in which the undulating engrammatic wave form may include the left temporo-parietal conceptual speech centers. When the engrammatic wave form passes through this temporo-parietal conceptual speech center, whether or not it produces motor speech, we are explicitly "conscious" of the engrammatic integration as an idea, a perception, a wish or whatever.

When a new wave form emerges from the interaction of several engrams, and this new engram passes through the conceptual speech center, a new *verbal* unity enters consciousness. It has apparently been synthesized from the different components which entered the neurophysiological interaction. This single creative verbal "symbol-image," which may be a word, phrase or formula, then represents an integration of all the sensations and conceptualizations which entered the neurophysiological interaction.

The Final Common Explicit Conceptual Pathway

Finding unities in nature and embodying these unities into single symbols has been the basis of the development of language, a prerequisite for human culture. For each individual, the creation and use of such symbolic unities is the basis of his explicit conceptualization and therefore of his intelligence. As we have seen, this process apparently *must* involve the left temporo-parietal cortex. Hence we may postulate that the left temporo-parietal cortex, which has been described as the conceptual speech center, is a kind of "common explicit conceptual (or intellectual) pathway."

The principle of the final common pathway was first enunciated by Sherrington, in connection with the anterior horn cell of the spinal cord, the motoneuron, which is the ultimate neurological determinant of muscular contraction. "The final link in the reflex arc, the motoneuron, is . . . called the final common path," write Best and Taylor.[9] "Each final common path is as the stem of a funnel of which the numerous afferent paths represent the expanded portion."

Just as the motoneuron is the "stem" of the "funnel" determining motor activity, so can we see the left temporo-parietal cortex as almost the "stem" of the "funnel" determining explicit conceptualization, inasmuch as it apparently governs simultaneous verbal synthesis. But just as the final motor path produces environmental consequences which must be considered, so does the final explicit conceptual path produce motor consequence, including autonomic speech and writing responses, which must similarly be taken into account.

As pointed out above, stimuli enter the central nervous system in a relatively small number of ways, "with each of the sense organs (reporting)," as Eccles[4] described, "on its own lines . . . to specific regions of the cortex." These specific receptor regions in the cortex can also be compared to the stems of a small number of sensory funnels; damage to any one permanently impairs percep-

tion of the particular sensory modality involved.

The many simultaneous stimuli then evoke reverberating engrammatic circuits, involving all parts of the brain, through which the various stimuli are integrated with the relevant reflexes and memories. This interaction continues until a motor response is evoked through the final common motor pathway.

When, however,, we are dealing with explicit human thought, rather than with motor response, a different and intermediate "funnel stem" or "common pathway" is apparently involved. For the engrammatic interactions to produce explicit concepts, of which the subject is consciously aware, the small number of synthetic wave forms resulting from this interaction *must* pass through cells in the conceptual center in the left temporo-parietal cortex. This area thus seems to function as the stem of the funnel of explicit conceptual processes, in a fashion analogous to the anterior horn cell "stem" of the "funnel" of motor processes.

The Use of the New Conceptual Unities

As mentioned above, finding unities in nature and embodying these unities into single symbols has been the basis of the development of language, a prerequisite for human culture. But an infinite number of unities can be found between any two phenomena, should only seek them; in mathematical terms, an infinite number of curves can be drawn through any two points. Thus a spade can be a spade, or an agricultural implement. It can even be a phallic symbol if one seeks to relate all phenomena to the genitals.

The search for unities has value to society, and investigative curiosity brings satisfaction to the creative man only because, ultimately, some of these new unities may have some human significance and value. Basic human values arise from basic human needs,, the most basic of which is the need for survival and progress of the species. Hence new unities have significance only when in some way they ultimately enhance human survival, progress and growth.

Men, like all animals, are faced with problems almost every minute of their lives. A problem is a situation to which various responses can be made, but in which the different responses will be of varying survival value to the organism or species. Problem-solving is the determination of a satisfactory response. In solving a problem optimally, all the significant data in a situation will be correctly integrated in order to determine the particular response which is most satisfactory. This optimal integration produces the *best* solution to the specific problem.

Creativity is an advanced kind of problem-solving, in which the problem is relatively unspecified: to find a new connection among existing phenomena. Often this becomes a matter of finding the "best" connection among the phenomena. Scientific method is man's conscious codification of the unconscious neurophysiological processes employed by all animals in solving problems. Let us therefore examine the role of creativity in scientific method.

Creativity and Scientific Method

The human phenomenon known as scientific method has three steps. The first is the gathering of data, the second is the tentative formulation of new creative connections among the data: i.e., the formulation of hypotheses, and the third is the testing of the hypotheses thus created.

The method of gathering data is of course a function of the society within which this process takes place. The physical tools used for the gathering of data and the intellectual concepts used for its presentation and processing are determined by the level of civilization in which they occur. Inasmuch as the human mind can deal with only a limited number of separate data at one time, the development of ever more inclusive symbols, through which more and more individual pieces of data can be singly represented, makes it possible for ever increasing numbers of data to be included in a particular individual integration.

Similarly with the testing of hypotheses: this must be done using the tools at hand, or through the creation of new tools (or

perhaps new concepts also). The testing of hypotheses can go on at various levels of practicality, ranging from logical proof, to scientific proof, to direct application. Thus the Einstein hypothesis, defining the relationship between matter and energy, was proven first logically, then confirmed experimentally by study of the deviation of light from stars when it passed close to the sun; this was a matter of interest primarily to astronomers and other scientists. Later, it was proved in a manner much more relevant to us all—by atomic and nuclear explosions.

The collection of data and the testing of hypotheses are both processes taking place within the full, verbalizable consciousness of the investigator. He must be verbalizably conscious of the data which he is gathering, if it is to enter his mind for subsequent creative interaction; indeed, usually the data is written, and consequently more readily returnable to conscious awareness. Similarly, after his hypothesis has been formulated, he must define it explicitly, and explicitly demonstrate exactly how he proposes to test it, so that his tests can subsequently be repeated by other workers. Hence both the collection of data and the testing of hypotheses, the first and third steps of scientific method as we have defined it, are conscious, verbal and explicit.

The Creation of New Hypotheses: A Less Explicitly Conscious Process

The psychological processes involved in making the connections between previously unrelated data through the creative construction of hypotheses are quite different from, and much less verbally conscious than, those involved in gathering the data or testing the hypotheses. It is a matter of everyday experience that the process of problem-solving, the formulation of new hypotheses or integrations, often takes place outside of explicit consciousness. Indeed, it may well be true that the more difficult a problem is, the more likely it is to be solved outside of explicit consciousness, and for the solution then to enter explicit consciousness in relatively finished form.

We have all had the experience of having addressed ourselves unsuccessfully to a seemingly insoluble problem. After having put it away for a while, or after having "slept on it," when we return to it, we find that the solution has suddenly appeared. Such problem solving is the result of the central nervous system's metaphorically continuing to wrestle with the problem outside of consciousness. Put into more precise terms, the interaction of the different engrammatic circuits representing aspects of the problem continues, even though the problem is outside consciousness. Perhaps the more painful or bothersome an unsolved problem is, the greater the likelihood of its producing prolonged extra-conscious engrammatic reverberation within the central nervous system; the less painful it is, the more easily damped will its reverberations be.

The Evocation of Unconscious Solutions Into Consciousness

The unconscious process of the formation of one new engram from several old ones has been described, again by Eccles.[4]

> "We may surmise," he writes, "that the 'subconscious operation of the mind' involves the intense and unimaginably complex interplay of the engrams. We have seen that on repeated activation (e.g., as in studying—NSL) there tends to be a progressive change in their congealed patterns resulting particularly from interaction with other patterns. Thus we can expect that new patterns will arise during the subconscious phase of the effort."

These new patterns are the neurophysiological bases of the creative product. How does this new, but unconscious, creative product become conscious? Eccles suggests:

> "Should an emergent pattern combine and transcend the existent patterns, we may expect some resonant-like intensification of activity in the cortex, which will bring this pattern to conscious attention. There it comes to light as a new idea."

I wonder if it is necessary to postulate this "resonant-like intensification of activity in the cortex," which, as it were, "forces" the new idea into consciousness. Perhaps it would be simpler to consider the new integration as being evoked into verbal con-

sciousness via conscious awareness of the problem, or of something related to it. Seeing his desk strewn with papers might, for example, remind the investigator of the problem with which he had been struggling. As the result of his being reminded of the problem, the new neurophysiological integration, the "solution" which had been achieved extra-consciously during the period he was not explicitly conscious of the problem, can then be evoked into clear verbalizable consciousness.

Freud pointed out how in dreams a part can represent the whole, and how associative chains can be used to decipher them. Such representations of the whole by one of its parts are indeed basic to everyday communication patterns.

Since the part can represent the whole, it can also *evoke* the whole. Hence consciousness of a part of a problem can *evoke* consciousness of the whole problem, through the above-mentioned associative mechanisms, the physiology of which has been indicated by Eccles. Hence if a neurophysiological "solution" to a problem has been arrived at outside of consciousness, it is perhaps more likely that it is then *evoked* into consciousness via consciousness of one of its parts, rather than being "forced" into consciousness as Eccles proposes.

This kind of extra-conscious problem-solving is very common, and is indeed, I suspect, the way in which many creative hypotheses are formulated.

Consciousness and Wakefulness

Consciousness and wakefulness are related to one another, but are by no means identical. Psychoanalysts talk about "dream consciousness," and I believe they are correct. Kekule's recognition of the benzene ring hypothesis in a dream is a noteworthy example of the fact that dream consciousness can be accurate and valuable (even without interpretation); Coleridge's composition of "Kubla Khan" also in a dream is another example.

Consciousness has here been defined as "the subjective reflection of those neurophysiological engrammatic circuits which, at a particular moment, include cells within the conceptual center of the brain." Hence dreams are a form of consciousness, inàsmuch as they are also the subjective reflection of the neurophysiological processes, whose circuits include conceptual center cells, which are involved in preparing to make motor choices, a process which proceeds even during sleep.

Wakefulness implies a certain level of attention. "What attention does is to use the discriminative power of the cortex to focus consciousness upon a certain perceptual experience at any particular moment," writes Brain.[2] In neurophysiological terms, which would be applicable also to animals, attention selectively increases the responsivity of the organism to certain stimuli or combinations of stimuli. Wakefulness or vigilance can then be seen as a measure of the general responsivity of the organism, which will be related to the amount of painful or fearful stimulation it is experiencing, or has recently experienced. When the eyes are closed there are fewer visual stimuli and sleep is more likely to occur.

We can distinguish between wakefulness and consciousness in humans but can we do so in animals? Some mammals seem to dream but does this mean they are "conscious"? All we can say is that the same kind of neurophysiological processes occur in them as in us, except on a much simpler level, and without the existence of any speech or cenceptual centers which might be included in the circuitry. In animals, therefore, all we can measure is responsivity, general and selective. In the sense of an animal's being subjectively "aware," or conscious, as we humans are, we have no proof which is not anthropomorphic. Hence it would appear best to limit to the human species the use of the word conscious—without quotation marks.

The Emotional Aspect of Thinking: The Pleasure and Pain Systems

How we react to present stimuli and situations is determined by our past experience, from which we determine the "meaning" of the stimuli. The past experience of any hu-

man includes the earlier experience of the human race as a whole, which is passed on to him through his parents and others from their culture.

But the cognitive process of determining the "meaning" of stimuli also has, as previously mentioned, a most important emotive aspect. Indeed, Sherrington pointed out that not only does every cognition have "potentially at least, an emotive value," but "along with that, conative effort as a further factor."[3] Hence emotionality involves at least a potential motor response. Cognition, therefore, involves emotionality, at least potentially, and emotionality involves striving, conative effort—a motor response—again, at least potentially.

What are the basic directions in which emotionality guides the organism? Lashley has suggested that "the psychological data must be analyzed . . . with reference to the patterns of activity which they represent."[10] What are the patterns of activity represented by emotionality?

Recent neurophysiological work suggests that there are two basic emotional qualities —pleasure and pain—governed by separate but interdigitating systems within the central nervous system. This concept, recently summarized by Lilly,[11] is based on the motor responses of animals to stimulation of electrodes implanted in different brain areas. The concept throws into strong doubt Fechner's one-variable hypothesis[12] which Freud adopted, that pleasure is the result of reduced "tension" while pain is the result of increased "tension." Lilly's two neurophysiological systems are apparently identical with Hess' ergotrophic and trophotropic systems.[13]

The idea that pleasure is different from the mere relief of pain was proposed by the psychoanalyst, Sandor Rado, as well as by many others before him. "This pleasure organization requires a term that reflects its biological nature and avoids confusion between the superior entity and its component parts," wrote Rado.[14] For our purposes, the two systems can be called the stress-relief-homeostasis, or pain system, and the growth-reward-bliss, or pleasure system. To return to Lashley's question: what patterns of activity are represented by these two systems?

In answer, we may suggest that the two systems, pain and pleasure, have evolved from increasingly fine nervous control of the basic motor patterns of withdrawal and approach, respectively. The pain system, which has priority, can be seen as having arisen out of the basic motor response of withdrawal, while the pleasure system can be seen as having developed phylogenetically from refinement of the basic motor response of approach.

All human and animal responses are the result of the interaction within the central nervous system of stimuli and the inborn reflexes and associated memories which they evoke. This integrative interaction determines first, whether the stimulus is painful, and warrants withdrawal, or pleasurable, warranting approach.

Comparative studies of the intensity of motor response to approach, and avoidance —eliciting stimuli, reveal a most significant difference between them. When the intensity of response is plotted against distance from the stimulus, the slope of the avoidance curve is much steeper than that of the approach curve.[15] From this we can surmise that avoidance responses, presumably governed by the "pain" system, are more intense and urgent, although of briefer persistence, than approval responses. The latter, presumably governed by the "pleasure" system, are on the other hand apparently gentler, but operative over greater distances.

(The second part of this article will appear in the September issue of *Diseases of the Nervous System.*)

Studies on Epinephrine Metal Complexes

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The isolations of a uranyl-epinephrine complex and molybdenum-epinephrine complex were reported by Cohen[1] in 1946 and chemical structures for these complexes were suggested. The demonstration that a serum vaso depressor material (VDM) is identical with the metalloprotein ferritin,[2] which is assayed by its antagonistic effect to epinephrine, has led to the suggestion that the mechanism for epinephrine transport in blood is by attachment to a metalloprotein. Antoniades et al.[3] have shown that most of the epinephrine and norepinephrine in human plasma is bound by protein fractions.

Cannon's[4] early observations implicated epinephrine in central nervous system function with reference to emotions and stress, and Funkenstein[5] has proposed that emotional state of psychotic patients may be related to the ratio of epinephrine to norepinephrine secretion. The provocative reports of Osmond and Smythies,[6] Hoffer, Osmond, and Smythies,[7] and Hoffer and Osmond,[8] have led to the proposal that schizophrenia is a disease in which there is an abnormal metabolic diversion of epinephrine to a toxic indole. Although other workers have not produced direct confirmation of this work of Hoffer et al., it has been suggested by Rinkel et al.[9] that an oxidation product of epinephrine might be hallucinogenic. In studies on urinary metabolites, Sulkowitch and Altschule[10] suggested that a difference existed between schizophrenics and controls with reference to an epinephrine metabolite. In addition, the work of Angel, Roberts, and Burkett[11] might be interpreted as suggesting such a difference.

In 1958, the isolation of a ferric iron-epinephrine complex and its effect on conditioned response in the rat were reported.[12] Since others have had difficulty in reproducing effects reported by Hoffer et al.,[7] it was felt that isolation of epinephrine oxidation products stabilized as metal chelates might enable us to obtain compounds with interesting behavioral effects. Recent reports indicating that cobalt[13] and magnesium[14] ions may alter the physiological effects of epinephrine "in vivo" gave additional encouragement to work in this direction.

In the present study a method for isolation of metallo-epinephrine complexes is presented. In addition, studies on toxicity, tolerance development, and physiological effects are outlined.

Methods and Material

The 1-epinephrine used in this study was obtained from Nutritional Biochemical Corporation. Other materials used were of analytic reagent grade obtained from commercial sources.

General Procedure for Synthesizing and Isolation of Epinephrine Metal Complexes

Suspend one millimole (183 mg.) of 1-epinephrine in 5 ml. of Methanol and add sufficient glacial acetic acid to dissolve the suspended epinephrine. Cool the resulting solution to 4°C. Prepare a solution of metal chloride in glacial acetic acid so that 5 ml. of solution contains 0.3 millimole of metal chloride. Cool the metal chloride solution to 20°C, then add it to the epinephrine solution with constant mixing. To the resulting mixture add 10 volumes of anhydrous diethyl ether. The addition of the ether causes the precipitation of the epinephrine metal complex. The precipitated material is transferred to a dry centrifuge tube. Care must be taken to prevent exposure of this material to a moist atmosphere. The material is centrifuged for two minutes at 1000 r.p.m., the supernatant fluid is discarded, and the residue immediately resuspended in anhydrous ether and centrifuged again. The ether supernatant fluid is discarded and the precipi-

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tate is immediately resuspended in anhydrous ether and centrifuged again. The ether supernatant fluid is discarded, and the precipitate is immediately resuspended in anhydrous ether. This washing procedure is repeated one more time, and the residue is then dried in vacuo for several hours. The resulting product is readily soluble in water and in the dry state appears to be stable at room temperature.

The preparation of an epinephrine cobalt (A) complex and an epinephrine derivative-iron complex can be accomplished utilizing the above procedure. A second epinephrine derivative cobalt (B) complex can be prepared by the above procedure with the following alterations: Immediately after addition of the cobaltous chloride glacial acetic acid solution to the epinephrine solution, one adds 0.2 ml. of 30% hydrogen peroxide. The resulting solution is mixed and permitted to stand in an ice bath for a period of 10 minutes before addition of the 10 volumes of anhydrous ether. The washing and drying is then done as in the above procedure.

The acetate content of each of the different complexes was determined by the azeotropic distillation method described by Schicktanz et al.[15] Nitrogen was determined by using the Kjeldahl method. The epinephrine content was estimated on the basis of nitrogen as well as by comparing the absorbancy values of the complexes with 1-epinephrine at a wavelength of 280 mu using the Beckman DK-1 recording spectrophotometer. Iron and cobalt were determined using methods described by Mellan.[16]

Results

The complexes described in this report are all readily soluble in water. The iron complex is a purple solid which melts with decomposition at 170°-172°C. In fresh aqueous solution it has a visible absorption maximum at 565 mu which is pH dependent, and the fact that color changes due to alteration of pH are reversible, particularly in the range of pH 4.0 to 9.0, suggests that this complex is relatively stable.

The cobalt (A) complex, isolated by the same procedure as the iron complex, is a pale blue solid which appears to decompose in the range of 75° to 80°C. The aqueous solution is very faintly pink but undergoes rapid oxidation in the presence of atmospheric oxygen. The cobalt (B) complex is an olive green solid which melts over a range from 102° to 120°C. The aqueous solution is pale yellow with a visible absorption maximum at 395 mu.

In Table I, the percent composition of each of the complexes is presented. The value listed for each constituent is the average plus or minus the standard deviation of duplicate determinations on six individually prepared samples of material. The empirical formula of each compound calculated on the basis of percent composition is also presented.

TABLE I

Composition of Metallo-Epinephrine Complexes

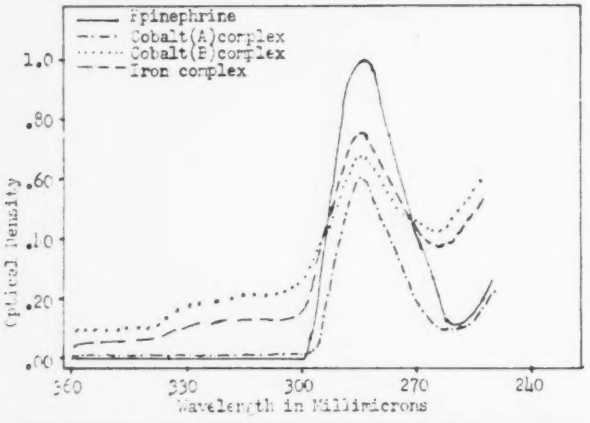
Metal Component	Percent Metal	Percent Epinephrine	Percent Acetate	Empirical Formula*
Iron	7.9 ± .1	75.8 ± .8	16.7 ± .4	$FeEp_3Ac_2$
Cobalt A	7.8 ± .1	60.5 ± .8	31.9 ± .7	$Co_2Ep_5Ac_8$
Cobalt B	10.9 ± .2	67.2 ± 1.1	22.0 ± .6	$CoEp_2Ac_2$

*Ep = Epinephrine, Ac = Acetate

In Figure 1, the utra violet absorption spectrum of epinephrine is compared with that of the three metal complexes. If one compares these with the spectra of hydroquinone and quinone, the suggestion arises that the cobalt (A) complex is comparable to hydroquinone and epinephrine while the iron complex may be a semi-quinone and the cobalt (B) complex a quinone.

In preliminary studies it was established that the LD-50 for intraperitoneal injection into adult male rats of Wistar strain is approximately 2.3 mg./kg. for the iron-epinephrine complex and 2.5 mg./kg. for the cobalt (A) complex. In addition, it was noted that pretreatment with sublethal doses of either compound caused a significant increase in tolerance to subsequent injections of either complex and even increased tolerance to epinephrine. Data supporting these

Figure 1. Ultraviolet absorption spectra of epinephrine and metallo-epinephrine complexes. Each solution contains 67 μg/ml of material dissolved in 0.1 N sulfuric acid solution.



observations are presented in Table II where it may be seen by pretreatment with sublethal doses of the complexes one obtains approximately 85 per cent survival when injecting 4.0 mg./kg. iron-epinephrine complex or 6.0 mg./kg. of the cobalt (A) epinephrine complex. Doses of this magnitude without pretreatment usually cause 100 per cent mortality. In Table II, it is shown that of 17 rats in which tolerance to the iron-epinephrine complex was established, injection of epinephrine (1.5 mg./kg.) caused death in nine animals or 53% of this group. Of the group in which tolerance to the cobalt (A) complex was established a similar dose of epinephrine (1.5 mg./kg.) caused only 39% fatality. In the control group, injection with epinephrine (1.5 mg./kg.) caused 95% fatality.

The iron-epinephrine complex was tested for pressor and depressor activity in the anesthetized dog before and after adrenergic blockade with regitine. The results indicate that the iron-epinephrine complex is 0.76 as potent as epinephrine in its effect on blood pressure in the dog. Reference to Table I shows the "epinephrine" content to be in close agreement with this figure.

In an attempt to find possible effects on brain function, both the iron-epinephrine and cobalt (A) epinephrine complex have been administered intravenously to rhesus monkeys. Intravenous doses of 200 to 400 μg./kg. produced no observable discomfort or change, and doses as high as 800 μg./kg. produced only a transient blanching of the ears and face. None of the injections caused any significant alteration of the electroencephalogram which was traced from electrodes implanted in cortical and subcortical structures. The high tolerance of the rhesus monkey to the intravenous doses of these complexes may represent a species difference in reactivity. It is interesting to note that the amounts of the complexes per kilogram administered to the monkeys ranged from two to four times the LD-100 for intravenous administration to the rat and the rabbit.

TABLE II

Effect of Pretreatment with Sub-Lethal Doses of Metallo-Epinephrine Complexes on Survival of Rats

No. of Rats	Pretreatment	Material for Treatment	Dose Mg./Kg.	No. of Survivors
20	None	Iron-complex	4.0	0
20	1.0; 2.0; 3.0*	Iron-complex	4.0	17
20	None	Cobalt (A) complex	6.0	1
20	2.0; 3.0; 4.0*	Cobalt (A) complex	6.0	19

*Rats in these groups were pretreated with the three doses indicated in Mg./Kg. The pretreatment schedule consisted of lowest dose on day 1, second dose on day 5, and third dose on day 9. The comparative studies, i.e. 4.0 Mg./Kg. dose of Iron-complex and 6.0 Mg./Kg. dose of Cobalt (A) complex, were carried out on day 14.

TABLE III

Effect of Pretreatment with Metallo-Epinephrine Complexes on Toxicity of Epinephrine for the Rat

No. of Rats	Pre-treatments*	Mg./Kg. Epinephrine Administered	No. of Survivors
17	Iron-complex	1.5	8
18	Cobalt (A) complex	1.5	11
20	None	1.5	1
16	Epinephrine 0.3; 0.5; 0.75 Mg./Kg.	1.5	0

*See Table II for pretreatment schedule and dosages. Animals in first and second group were survivors indicated in Table II.

Discussion

In continuing studies on metal derivatives of epinephrine and epinephrine oxidation products, we have isolated complexes of magnesium, aluminum, nickel, copper, zinc, silver, as well as a few others, and studies on these will be reported. The copper and the silver derivatives which we have isolated are much less stable, even in the dry state, than other products of this series.

It seems remotely possible that Hoffer, Osmond, and Smythies[7] may have been using adrenochrome containing a silver complex of an, as yet, unknown compound in the studies in which they reported hallucinogenic activity for adrenochrome. This is plausible from a chemical standpoint since silver oxide was used as an oxidizing agent in preparing the adrenochrome which they used, and it might also account for lack of confirmation of their work by others.[9,17] We are attempting to test such a possibility.

Summary

1. A general method for isolation of metal complexes of epinephrine and epinephrine oxidation products is presented.

2. The composition of three such complexes is established.

3. The rat is able to rapidly develop tolerance to these complexes, and once tolerance is established, the rat becomes more resistant to toxic effects of epinephrine.

4. In intravenous doses up to 800 micrograms per kilogram, the iron and cobalt (A) complexes do not significantly alter the electroencephalogram of the rhesus monkey with leads to cortical and subcortical structures.

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REFERENCES

1. Cohen, G. N.: Existance et Constitution d'un Complexe Adrenalino-uranylique. *Compt. rend.*, 222:890, 1946.
2. Mazur, A., and Shorr, E.: Hepatorenal Factors in Circulatory Homeostasis; Identification of Hepatic Vasodepressor Substance, VDM, with Ferritin. *J. Biol. Chem.*, 176:771, 1948.
3. Antoniades, H. N., Goldfein, A., Zileli, S., and Elmadjian, F.: Transport of Epinephrine and Norepinephrine in Human Plasma. *Proc. Soc. Exptl. Biol. Med.*, 97:11, 1958.
4. Cannon, W. B.: "Bodily Changes in Pain, Hunger, Fear and Rage." Boston, *Charles T. Branford Company*, 1929.
5. Funkenstein, D. H.: Nor-epinephrine-like and Epinephrine-like Substances in Relation to Human Behavior. *J. Nerv. & Ment. Dis.*, 124:58, 1956.
6. Osmond, H., and Smythies, M. B.: Schizophrenia: A New Approach. *J. Ment. Sci.*, 98:309, 1952.
7. Hoffer, A., Osmond, H., and Smythies, J.: Schizophrenia: A New Approach II. *J. Ment. Sci.*, 100:29, 1954.
8. Hoffer, A., and Osmond, H.: Schizophrenia—An Autonomic Disease. *J. Nerv. & Ment. Dis.*, 122: 448, 1955.
9. Rinkel, M., Hyde, R. W., and Solomon, H. D.: Experimental Psychiatry I: A Chemical Concept of Psychosis. *Dis. Nerv. Syst.*, 15:259, 1954.
10. Sulkowitch, H., and Altschule, M. D.: Urinary "Epinephrines" in Patients with Mental and Emotional Disorders. *Arch. Gen. Psychiat.*, 1: 108, 1959.
11. Angel, Chas., Roberts, A. J., and Burkett, M. L.: Spectrophotometric Studies on Urinary Constituents of Schizophrenic Subjects. *Dis. Nerv. Syst.*, 20:292, 1959.
12. Angel, Chas., Carpenter, P. B., Carpenter, J. T., and Lafferty, C. R.: Studies on an Adrenaline Oxidation Product. *Presented at Ann. V. A. Med. Res. Conf.*, Dec. 1958, Memphis, Tenn.
13. Szilagyi, T., Kocsar, L., Szatai, I.: Effects of Cobalt Ion on Adrenalin Reactions. *Acta Physiol. Hung.*, 11:409, 1957.
14. Gray, I., Jordan, W. J., Goldberg, N. D., and Cash, W. D.: Mechanism of the Protective Action of Magnesium in Mechanical Trauma Involving Epinephrine and Norepinephrine. *Am. J. Physiol.*, 189:229, 1957.
15. Schicktanz, S. T., Steele, W. I., and Blaisdell, A. C.: *Ind. & Eng. Chem. Anal. Ed.*, 12:320, 1940.
16. Mellan, I.: "Organic Reagents in Inorganic Analysis." Philadelphia, *Blakiston Co.*, 1941.
17. Heath, R. G., and Leach, B. L.: Personal Communication.

The Safety Factor in Electrotherapy

NEVILLE MURRAY, M.D.

It is well known that unmodified electroconvulsive procedure frequently has a drastic effect upon a patient's bony structures. A recent report by McNichol describes a fatality due to "Crush Syndrome" as a delayed complication to electrotherapy involving bilateral femoral fracture. I shall not dwell upon the unfavorable influence such circumstances exert upon psychiatric public relations. Nevertheless, unmodified procedures are still widely employed and supported. Those puritans who advocate this practice justify their attitude with the claim that simplicity is the key note of safety. They show antagonism towards contemporary modifications in technique designed to reduce side-effects by insisting that the complications are of minimal significance. They insist that the varying modalities and auxiliary chemical substances employed in the new techniques bring with them a legacy of unjustified and unnecessary hazard.

The purists have cast aspersions on the use of phenothiazine and other psychotropic substances in association with electrotherapy despite their benefit in controlling post treatment agitation and anxiety as reported by Ayd and indirectly by Bogen-Tietz. I wish to report the results of an investigation concerning the effect of intravenous premedication with such a substance.

A group of 50 patients of both sexes ranging in age from 28 to 84, suffering from severe depression, was studied. Observations were made on 497 individual treatments. Prior to electroconvulsive therapy each patient was given an intravenous injection of 50 mg. of promazine (Sparine) followed by a dose of 200 to 300 mg. of Nembutal, 1/50 of a grain of atropine sulfate and 20 mg. of succinylcholine dichloride (Anectine), by the same route. Electrostimulation was applied using apparatus delivering an AC current of 140 volts for .6 of a second. Blood pressure estimations were made prior to injection and for two hours following treatment at 30 minute intervals.

No significant blood pressure fluctuations or cardiovascular abnormalities in any of the patients were noted. The effects upon behavior, prolongation of sleep and diminution of post treatment agitation, were attributed to the potentiating action of the promazine upon the barbiturate. Some 40 to 60 seconds after the intravenous administration of the promazine, coughing would occur. This was short lived and never caused respiratory embarrassment. Its origin was thought to be due to the potentiation of the drying of the atropine on the bronchial secretions.

Since the original investigation I have successfully carried out similar techniques employing other chemically allied substances including trifluprom azine and perphenazine in appropriate doses. The same premedication was employed with combined AC and uni-directional techniques without incident. It is concluded that intravenous promazine premedication is a safe and effective agent in the control of post treatment agitation and excitement. It is of particular value in treating patients with a history of excessive drug or alcoholic habits who often show post treatment excitement. Similar procedures with patients who concurrently were receiving Marsalid in daily doses of 150 mg. by mouth have been utilized in 50 additional patients, again without complication. The intravenous method of administration of promazine is preferable in controlling post shock excitement in view of the advantages afforded by peak dosage during the period of maximal excitation. To allow such excitement to remain uncontrolled is an unnecessary hazard.

The physical well-being of the patient is the first matter for consideration in the administration of safe electrotherapy. No psychiatric patient can be properly evaluated until a comprehensive physical and neuro-

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logical examination has been carried out. Even if this be normal, in those patients over 50 years of age, an electrocardiogram is usually and advisedly performed. Abnormal electrocardiographic findings in themselves need not be considered a bar to treatment. I should like to quote from a communication by Dr. Henry Leopold, a distinguished cardiologist and valued colleague:

"Those cases that have had recent coronary occlusion are certainly not candidates for electrotherapy. Those cases that have concomitant aortic stenosis on a rheumatic basis are dubious candidates. Those cases of active myocarditis whether the etiology be on a viral basis or on an obscure basis are not candidates for electroshock therapy.

"The electrocardiogram is the most valuable single aid in the selection of candidates for this type of treatment. A number of types of heart block exist, those affecting the sinus node and those of conduction between the sinus node and the AV node which may be either first, second, or third degree heart block, those affecting the bundle of Hiss which are unusual and difficult to detect, left and right bundlebranch blocks and the so-called arborization of peri infarction block. Any of these diagnoses sound ominous to the psychiatrist, so a few words must be said in connection with them. Peri infarction block, unless accompanied by recent coronary occlusion or following recent coronary occlusion, is not a contra-indication to therapy. Complete heart block is not a contra-indication to therapy and the other types of block of more minor character certainly are not contra-indications. The electrocardiogram is an excellent guide as to healing of the infarction, and as a general rule four weeks after coronary occlusion can be considered a safe time to use stimulative therapy if necessary."

The changes in electrical modality in recent years have brought about a variety of techniques. AC currents are still successfully and commonly employed in the treatment of severe depression often accompanied by post-convulsive doses of uni-directional current designed to decrease amnesia and reduce post-shock excitement. These unidirectional techniques involve a more prolonged administration of electrical impulse. This would seem to be less well tolerated in older persons. It is then considered unwise to use prolonged administration of electrostimulation of any sort in cases of suspect cardiac or respiratory disease. In the reports of fatality which have been reviewed, notably by Impastato, cardiac or respiratory arrests are the most frequent offenders. These are vagal in origin. It follows that the keystone of any safe technique in electrotherapy lies in the prevention of excessive vagal stimulation and thus to preclude vagal asystole or vagal apnoea. The agent of choice is atropine sulfate in doses of 1/50 to 1/75th of a grain administered in such fashion as to persist at the time of the electrostimulus. Absorption of atropine is slow and its action comparatively short lived when given by the intramuscular route. As documented by Mushin et alia it is reported to take approximately 45 to 60 minutes to achieve maximum effect persisting during a 30 minute period. In large clinics and busy hospitals it is sometimes inconvenient, if not impossible, to ascertain the precise time of intramuscular injection given by even the most reliable assistants. It is not always possible to carry out treatment during the optimum period of 45 to 75 minutes after the administration of the drug. Therein lies the justification for my practice using the intravenous route immediately prior to treatment. Hejtmancik et alia have pointed out the value of atropine in their studies. In the same paper increased tendency to sinus rate changes were recorded in those patients given subconvulsive doses of electricity thus confirming contemporary clinical impressions. Atropine provides an essential protective field against vagal catastrophe whether asystole or apnoea.

Since the introduction of succinylcholine in electrotherapy the question of apnoea has become acute. It is of importance to differentiate between the apnoea induced by succinylcholine and that induced by excessive vagal stimulation. Apnoea from succinylcholine is a reversible and gradual phenomenon whereas apnoea induced by excess vagal stimulation is immediate and irremediable. There is no causal relationship between those two types of apnoea. It would seem unjust to incriminate succinylcholine as an offending agent in those fatal cases involving irreversible vagal apnoea where adequate and proper artificial resuscitative methods were available and applied. Wherever succinylcholine is used in electrother-

apy the use of an automatic breathing apparatus is essential. My choice is the "Handy Resuscitator" marketed by the National Cylinder Gas Company which administers a 13 millimeter mercury positive and 9 millimeter negative pressure in alternating sequence. When such an apparatus is utilized prolonged apnoea can be safely controlled. Gunn reports the administration of rapid intravenous doses up to 1,000 milligrams, given to patients without untoward effects. He found abnormal sensitivity to succinylcholine in one in 250 patients. In those subjects with low serum pseudo-cholinesterase activity, apnoea purposely produced was easily controlled with proper artificial respiration. Our anesthesiology colleagues give many thousands of milligrams intravenously to severely disabled and traumatized patients undergoing surgical procedures with apparent impunity. There seems little reason to assume that the combination of succinylcholine and electrostimulus is in some way lethal. As long as dysharmonic muscle movement response to electrostimulation is permitted there is danger of skeletal damage of unpredictable severity and consequence. When succinylcholine is properly employed the danger of skeletal damage is reduced.

In those cases suffering from major organic illness along with severe depression evaluation taxes the clinical wisdom and judgment of both consultant and psychiatrist. I choose the term "malignant depression" for this syndrome of combined severe organicity and self-destructive drive. The post-operative surgical emergency for example who becomes depressed and agitated and mutilates his surgical wound in his attempts at self-destruction. The depressed cardiac patient who in his agitation severely endangers his life with persistent psychomotor overactivity. The diabetic become suicidal and neglectful, refusing to maintain proper insulin dosage or diet. In my experience such cases can be successfully and safely treated with electrotherapy providing certain principles of patient evaluation are borne in mind and the selective use of modern treatment techniques is sagaciously made.

The general attitude of the internist toward electrotherapy often colors his deliberation as to the suitability of a questionable patient to undergo electroshock. Psychiatrists are aware of recent developments and modifications designed to reduce the stress of electrotherapy but the majority of doctors are familiar only with older unmodified techniques. Not knowing of any other rationale to explain the treatment process they consider it a punitive and brutal assault designed to galvanize the patient to a more acceptable pattern of behavior. Thus influenced the consultant may be liable to counsel the psychiatrist to administer treatment imprudently or conversely deny the patient advantages of electrotherapy on the basis of dangers stemming from his own unconscious processes rather than from a realistic appraisal of the actual safety factor in electotherapy.

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REFERENCES

1. McNichol, R.: *Am. J. of Psychiat.*, Vol. 115, No. 4, p. 346, October 1958.
2. Kalinowsky, L. B.: *Am. J. of Psychiat.*, Vol. 115, No. 4, p. 294, October 1958.
3. Ayd, F. J.: *Confinia Neurologica*, Vol. 16, No. 2/3, p. 168, 1956.
4. Bogen-Tietz, E., Powelson, K. D., Weber, J., and Wildhaber, J.: *Confinia Neurologica*, Vol. 18, No. 1, p. 57, 1958.
5. Leopold, H. N.: Personal Communication.
6. Impastato, D. J.: *Confinia Neurologica*, Vol. 16, No. 2/3, p. 152, 1956.
7. Muschin, W. W., Galloon, S., Lewis, F. E.: *Brit. Med. J.*, Vol. 11, No. 4837, p. 652, September 19th, 1953.
8. Hejtmancik, M. R., Bankhead, A. J., Herrmann, G. R.: *Am. Heart J.*, Vol. 37, No. 4, p. 790, April 1949.
9. Gunn, D. R.: Presentation, *Ontario Neuropsychiatric Assn.*, Ontario Hospital School, October 1955.

Procyclidine for Dystonia Caused by Phenothiazine Derivatives

GEORGE PAULSON, M.D.

Procyclidine (Kemadrin) for intravenous use has become available for research purposes. When several patients recently developed sudden severe dystonias following therapy with phenothiazine derivatives, intravenous procyclidine was tried clinically.

Typical Cases

The first patient was a 16-year-old boy with focal and petit mal epilepsy which usually occurred as a cluster of seizures. While being treated at home with an unknown amount of prochlorperazine (Compazine) for anxiety, he developed continuous twitches of the left foot and was admitted to hospital. The twitches were associated with waxy flexibility of the arms and inability to swallow or speak. His neck was rigid and hyperextended. He had a fixed stare and a fine tremor of his hands. Caffeine sodium benzoate, 0.5 gm., was given intravenously without effect, but 5 mg. of procyclidine given intravenously produced relief in five minutes. He was able to swallow and the rigidity decreased markedly. At this time he received 5 mg. trihexyphenidyl (Artane) orally. In 30 to 45 minutes the cervical and pharyngeal spasms recurred but in less severe form. Three hours later he was comfortable though twitching of the left leg continued for 24 hours.

The second patient, an anxious 28-year-old woman, developed muscle spasm with inability to protrude the tongue after 700 mg. of chlorpromazine (Thorazine) administered in four days. She was unable to articulate and was extremely frightened. There was cogwheel rigidity and a typical parkinsonian posture. Five mg. procyclidine given intravenously relieved all symptoms within 10 minuntes. The severe rigidity returned in 45 minutes, but after one additional injection of procyclidine and 5 mg. of oral trihexyphenidyl she felt well.

A 22-year-old girl treated with unknown amount of parenteral prochlorperazine for depression and agitation was admitted with "hysterical reaction." Every five minutes she had paroxysms of "a tight band around my neck" with a stertorous respiration and inability to retract the tongue. At times her tongue was clenched until it was blue-black. A few minutes after receiving 5 mg. of intravenous procyclidine the spasms dissipated and she became able to speak, though she still had increased tone of the cervical muscle group. Mild spasm of the cervical muscles recurred after an hours sleep. The patient slept again after 250 mg. of sodium amobarbital (Amytal) and on awakening the next morning there was no dystonia.

The fourth patient, a 16-year-old catatonic schizophrenic boy who had just completed 26 electric shock treatments developed dystonic symptoms after receiving 6 mg. of parenteral trifluoperazine (Stelazine) in 12 hours. There was extreme vertical deviation of gaze. An inconstant vertical nystagmus was present with the slower movement directed upward. His large muscular neck was almost completely retroflexed. Though there was transient relief of the neck posture when he lay down, in a few minutes his neck was flexed over the table. Intravenous procyclidine, 5 mg., relieved the neck spasm in 5 minutes. He became able to look straight ahead, but remained unable to look down for several hours.

Discussion

In 23 separate injections in 11 patients no significant side effects of intravenous procyclidine have been observed. A mild slowing of pulse occurred in several patients. Blood pressures did not change. The patients experienced only a sense of relief after the medication was given.

The transient nature of the dystonic syndrome and the anxiety and suggestibility of many of these patients make evaluation of therapy difficult. Caffeine sodium benzoate has been clearly beneficial in phenothiazine dystonia,[1] sedative drugs benefit some patients,[2] and recently dyphenhydramine (Benadryl) afforded prompt relief in one case.[3] Intravenous procyclidine is another emergency treatment of severe dystonia resulting from phenothiazine derivatives.

Intravenous procyclidine has been used clinically in several other situations. Two of five patients with post-encephalitic or drug induced parkinsonism were temporarily improved by intravenous procyclidine. All five patients were on oral anti-Parkinson

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The drug, procyclidine, used in this study was supplied by Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y., under their tradename Kemadrin.

drugs, and the two patients benefited by intravenous procyclidine were also benefited by additional oral medication. In one instance the drug seemed helpful in separating stereotyped movements of schizophrenia from a Parkinson tremor. Oculogyric crises in one patient with post-encephalitic parkinsonism were intractable to intravenous procyclidine.

It is our conclusion that intravenous procyclidine has usefulness in treatment of severe dystonia resulting from the administration of phenothiazine derivatives.

REFERENCES

1. Freyhan, F. A.: Discussion of Clinical Clues as to Mode of Action of Ataractic Drugs: Round Table. *Psychiat. Quart.*, 32:41-84, Jan. 1958.
2. Christian, C. D., and Paulson, G.: Severe Motility Disturbance After Small Doses of Prochlorperazine. *New Eng. J. Med.*, 259:828-830, Oct. 1958.
3. Waugh, W. H., and Metts, J. C.: Severe Extrapyramidal Motor Activity Induced by Prochlorperazine. *New Eng. J. Med.*, 262:353-354, Feb. 1960.

Calming Effect of the Monoamine Oxidase Inhibitors

ROBERT ARNOT, M.D.

It has been observed that there are certain calming effects felt subjectively by patients taking the monoamine oxidase inhibitors, particularly iproniazid (Marsilid) and isocarboxazid (Marplan). The literature describes these drugs as antidepressants, energizers, psychoenergizers, and recommends their use in depressions. But clinical experience has demonstrated that these drugs also have a definite role in the treatment of chronic psychoneuroses, especially those with chronic anxiety or with obsessive-compulsive symptoms. The improvement observed is different from that previously recorded with the barbiturates, phenothiazines or meprobamate.

These patients complain of combinations of anxiety, tension, depression, multiple somatic pains, gastric distress, nausea, morbid thoughts, and fatigue. When the monoamine oxidase inhibitors are effective, these symptoms are alleviated to various degrees. "I notice a great calm and freedom from anxiety," reported one 56-year-old business man with a history of six years of intensive psychotherapy. He added, "I do things better." "I have a heightening of my awareness of things." "No anxiety dreams." "I notice that I've had a more normal, refreshing sleep." Other psychoneurotics stress that they have a feeling of strength and solidarity. They state that they think more clearly and effectively.

The calming effect may be noticed specifically as a lessening of gastric tension. These chronic psychoneurotics have been on many medications and can therefore act as their own controls. The patients emphasize how the "calm" and "poise" are different from previous medications. One woman, who responded well to the monoamine oxidase inhibitor, said, "I was afraid this would make me dull like the Thorazine (chlorpromazine) that I had been on before."

Many explanations for the calming effect are possible. With the elevation of the depression the anxiety is reduced. (These two symptoms often increase or decrease together rather than divergently.) With the experience of increased psychic energy, the patients meet their psychological problems more effectively. With relief from physical demands, the need for sympathetic adrenal overactivity is reduced.[1]

Alexander[2] has reported that chlorpromazine and iproniazid give a similar decreased response to conditioned-reflex stimuli. The determination of the actual cause of the calming effect will require further experimentation.

BIBLIOGRAPHY

1. Arnot, R.: *Dis. Nerv. Syst.*, 20:49, May 1959 Supp.
2. Alexander, L., and Lipsett, S.: *Dis. Nerv. Syst.*, 20:26, Aug. 1959 Supp.

The Psychiatrist and the Internist

TRACEY H. MCCARLEY, M.D.

Because of the prevalence of emotional illness, its treatment (early treatment may be considered prevention) obviously cannot be handled by the psychiatrist alone. As many as 70% of patients visiting a medical outpatient department suffer from some emotional illness. Because he sees so many patients and often at an early stage of an illness, the nonpsychiatric practitioner can provide important care. Other factors also place a physician in the role of psychotherapist, i.e., lack of psychiatrists in the area and the patient's refusal to consult a psychiatrist. With the increasing attention to this aspect of medicine in recent years, both intensive and extensive courses in psychiatry or comprehensive medicine have been introduced into medical curricula.

What of the physicians who graduated before these changes? The need for this training was considered when the Langley Porter Neuropsychiatric Institute set up in the outpatient department a postgraduate course in psychiatry to give the physician experience in supervised psychotherapy.

My paper reviews some experiences in the supervision of one of these students and interprets these experiences. The excerpts from the work contrast the way the nonpsychiatric physician tries to use the doctor-patient relationship for psychotherapeutic purposes with the way the psychiatrist does. These contrasts are typical of many clinical experiences.

The physician-student, a mature, successful practitioner of internal medicine, had for years been interested in psychiatry and had frequently referred patients for psychiatric care. The patient assigned to him, a woman of 30, complained of compulsive eating. She had not worked for 11 years and had almost no human relationships except her widowed mother, with whom she lived. She had twice started psychotherapy but had stopped treatment after three or four interviews. She resisted the idea that talking would do her any good and wanted us to tell her what kind of job to get; in fact, to get a job for her.

The question, to recur often over subsequent weeks, arose after the first interview conducted with the physician-student sitting in as an observer. Although the patient's history had been somewhat actively elicited, Dr. C., the physician-student, was struck by the silences and periods of waiting for the patient to follow her own trend of thought. Discussion of this point led him to consider the differences in goals between a psychotherapeutic interview and history taking in the internist's office, where the physician may have only 15 minutes with his patient while several more are waiting. This physician cannot listen to the detailed, oftentimes hesitant, self-revelations which make up the core of good psychotherapy. When a conscientious physician ignores his schedule to listen to someone in need, he feels harassed at keeping someone else waiting. This will prevent his giving full, relaxed attention to the patient and defeats the very purpose of psychotherapy. Nor is scheduling of longer visits for those patients who need more time the entire answer. The physician who schedules extra time for a patient without charging accordingly is cheating himself and the patient by such mismanagement of time. In general, only the physician with sufficient allotment of time and no one waiting can give the full force of his relaxed attention to the patient's pressing problems.

The nonpsychiatric physician usually aims in his contact (interview) with the patient to establish certain facts about the patient's health and arrive at a decision as to diagnosis and treatment which medical training greatly emphasizes in a physical disorder. As knowledge of bodily illness has progressed, this urgency has increased since there are so many treatable illnesses. Always the physician is concerned that he will miss some serious physical disorder; the great increase in malpractice suits adds to the pressure that he miss nothing. As a result the physician is engaged in a search; and his

ally in this search is the mind of the patient. It is through the psyche that the patient reports and describes his symptoms. When neurotic processes are at work, this reporting becomes inconsistent, distorted, inhibited, exaggerated, absurdly circumstantial and in severe psychoses, virtually incomprehensible. For the physician whose aim is the detection of bodily disease, these defects in reporting become irritating obstacles. To look upon them as manifestations of disease and, indeed, clues to understanding the patient's disease requires a flexibility for the physician difficult to achieve. It is like that which Finesinger and Kellam[1] describe as desirable in the psychiatrist who must tailor his permissiveness to the needs and capabilities of each patient at a particular time.

The psychiatrist's habitual technique is free association with emphasis on passivity and permissiveness on the part of the therapist. Finesinger points out that the permissiveness must be modified in certain situations, for instance, when the psychiatrist decides whether a patient is well enough to leave the hospital.

The situation of the nonpsychiatric physician is just the opposite in that his habitual technique is one of authority and activity. He questions actively, he examines, he prescribes or he performs an operation. But with a patient whose illness is psychogenic or whose emotional problems have become of paramount importance in the course of a bodily disease, he must so shift his aims as to listen passively and uncritically in the way that the psychiatrist finds useful in these problems.

The physician-student, Dr. C., joked about the possibility of making this shift and not being able to shift back when he said (on the first day), "I'll be like the man who took his vacation on a river boat and decided he liked it so well he never went back to work."

Besides these problems of time schedules and differences in aims, there are the problems of the physician's personality. It was clear from my first meeting that Dr. C. is an habitually cheerful, hearty man with an active, restless curiosity and an eagerness to please. These traits largely determined his behavior during the therapy hours.

An illuminating exchange came at the end of the first interview which Dr. C. conducted alone. After he had told the patient that time was up she asked, "What about taking aptitude tests?" Although this question had already been raised and it had been indicated to the patient that her fear of going out to look for *any* job was the problem, Dr. C. answered, "We'll see about them." The next question came quickly, "Do we just talk?" His answer, "We'll be in a better position to help you if you talk," contained the misunderstanding of psychotherapy which every patient brings and which many physicians have. It implied that the patient's talking in the interview is a kind of obedient information-giving from which the doctor will construct a treatment to apply to the patient. This concept preserves the roles of the authoritarian physician and the passive, receptive patient. But the experience of psychotherapists is that in fact the talking constitutes the treatment. In this concept the patient collaborates in his own treatment.

Two more questions came from the patient, "Should I try to stop overeating?" "Should I worry about it?" Dr. C.'s answer, "Dont worry about it for now," tacitly accepted the role into which the patient wished to place the therapist. In effect it said, "Yes, I am the one who is to tell you what to worry about and what not to worry about." At the same time it encouraged the patient to make no conscious effort at curbing her impulses and thereby diminished her conscious experience of anxiety, which thus became less accessible to analysis. Sometimes one must assume this role with a patient in whom the anxiety is overwhelming; but this should be done out of therapeutic flexibility rather than the doctor's need not to frustrate his patient.

One more point about this series of questions; they should not have been answered at all since the hour had ended. Since he felt hurried, the physician could not consider his answers carefully and the result was non-therapeutic. To feel forced to answer

is to feel irritated; such irritation may if not recognized interfere with future objectivity. The therapist should have said, "Please bring these questions up next time." Such a statement did not occur to Dr. C., partially because of his understandable but therapeutically limiting need to please.

A common tendency of the nonpsychiatric physician is to ask one question after another, frequently of a leading nature. One example in the course of this work was the therapist's query, "Does your mother become angry when you overeat? This question suggests its own answer, so that an affirmative answer may indicate only that the patient wishes to please the therapist. It seldom leads to further disclosures since it is easy for the patient to give a quick yes or no answer and wait for the therapist to continue.

The patient said that she liked her doctor because he always had questions prepared to ask her. Of course the very dependent patient likes questions since they relieve him of the tension involved in trying to search himself. This sense of comfort with the physician often makes for an initial positive transference and a willingness to come for treatment. It may also result in reduced symptoms so long as the patient sees the physician, but does not foster the growth of genuine independence in the patient.

In the early supervisory hours we thoroughly discussed these examples and others of Dr. C.'s tendency to try to please his patient by assuming an authoritarian role, by asking many questions and, in general, assuming more than his share of the responsibility for making the interviews go. As I explained the benefits of a different role in the interview, Dr. C. became aware that the healthier part of his patient wanted less interference from him; e.g., he reported that she spoke of her irritation at "people who just keep asking questions." He felt she was referring to him. After the next hour Dr. C. reported with some surprise that the patient could talk more freely than before and had given him a clearer idea of the development of her difficulties. It is always hard to pinpoint what brings about such a shift in a patient, but it seems likely that after the supervisory discussions Dr. C. was more comfortable about sitting back and waiting for her to take the initiative.

On several occasions Dr. C. commented that he could see that he tended to talk too much and this was his biggest problem in effective psychotherapy. His parting words at the end of the course were to the effect that he would have to keep trying to be quiet and listen.

The case has signs of positive results despite the short duration of the experimental course. The basic good will, empathy and respect which this physician had in ample measure came through to the patient. The positive feelings engendered in the young woman enabled her to continue in treatment to the end of the course and to express enthusiasm as she had not been able to do previously. The physician, too, after the supervisory discussions could be somewhat less directive in the interviews. The result was fuller self-revelation by the patient and clearer understanding of her problems by the therapist, supervisor and the patient. By the end of the 12 weeks she had lost a few pounds. But more important, she gave evidence of being convinced that her problem resulted from unconscious fears and that her best chance of resolving these fears lay in psychotherapy. She saw also that much of the work on these fears was up to her and she began to understand that the therapist could only help in the process.

Conclusions

The material demonstrates that at first in his psychotherapeutic work with a patient the internist assumed the role of a benign but definitely authoritarian figure who was willing to lead his patient in the interview by repeated questions and by answers about her need to worry. She responded to his assumption of this role by liking him, by coming promptly and faithfully to her interviews and by attempting to curb her excessive eating. This simplification of what happened may serve as an outline of what psychotherapy tries to do, but psychotherapy with dis-

tinct limitations. Deep-seated problems are seldom touched by it. For example, it did not reach the girl's fear of going out into the workaday world and the connected dependent relationship with her mother. The fact that the improvement depends on the continued support of the physician is another limitation.

Supervision with detailed discussion of each hour made it possible for the physician-student to so modify his approach at times as to promote the self-revelation of the patient. The improvement which came in the form of her genuine recognition that some of the work of treatment was up to her may be a permanent gain since it may enable her to go on into further psychotherapy.

A most important learning experience for the physician-student was the recognition of his need to comply with the patient's spoken and unspoken demands that he direct the interviews. The interplay between a patient's wish to have an all-powerful father and a physician's wish to play such a role is probably a part of every therapeutic relationship. An awareness of these forces in actual practice gives the therapist a chance to promote genuine growth in his patient by avoiding the authoritarian stance.

Smith *et al.*[2] have commented on the reluctance of general practitioners to accept the relatively inactive role of the psychotherapist. The course they described, although it involved the physician's treating alcoholic patients in his office, did not provide individual supervision. Individual psychotherapeutic work with a patient, combined with individual supervision, seems the best way for the nonpsychiatric physician to examine carefully his usual approach to the emotionally disturbed patient. It is also the best way to demonstrate the beneficial effect of some change toward less activity and directiveness in the interviews.

This brief supervisory experience also shows the great difficulty which even a strongly motivated, interested nonpsychiatric physician may have in modifying his usual authoritarian approach to the patient. Yet such modification is essential for the physician to be effective as the psychotherapist he will be called upon to become again and again in the practice of almost any medical specialty.

Summary

In a 12-week postgraduate course in psychotherapy for nonpsychiatric physicians the emphasis was on individual work with a patient and supervision by an experienced psychotherapist. Differences between the psychiatrist's approach in an interview and that of a nonpsychiatric physician, seen in bold relief during this course, primarily had to do with the degree of activity in the interview, the nonpsychiatric physician generally being the more active.

A change in the patient toward freer self-expression followed discussion in supervisory hours of the physician-student's tendency to direct the interviews. Individual supervised psychotherapy has great value in orienting nonpsychiatric physicians to the psychotherapeutic attitudes.

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REFERENCES

1. Finesinger, Jacob E., and Kellam, Sheppard G.: *Am. J. Psychiat.*, 115:992-996, May 1959.
2. Smith, J. A., Strough, L. C., Wittson, C., and Mansfield, E.: *Am. J. Psychiat.*, 115:539-542, Dec. 1958.

Physical, Mental and Emotional Effects of Librium in Hospitalized Psychotic Patients

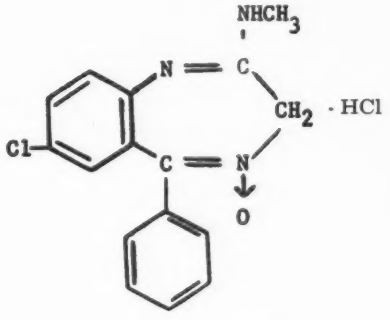
MARIE KERSHAW FRAIN, M.D.

The changes in mental hospitals resulting from the use of psychotherapeutic drugs have been much studied and discussed. In addition to a significant increase in the number of discharges[1] there is, within the hospital environment, greater order, cooperation and sociability.[2] Patients are more accessible to other forms of therapy; electroshock requirements have been significantly reduced.[1] The anxieties and fears of the patient are allayed and he can be taught to live with his psychosis.[3]

While a number of agents have proved effective in quieting the patient, none has been found suitable for the management of all types of mental disorders and for all degrees of severity. Certain drugs, e.g., chlorpromazine, appear better suited for the acutely disturbed, others such as meprobamate for the mildly disturbed. Chlorpromazine, while producing "tranquility," tends to reduce motor activity. This effect together with associated side reactions limits the usefulness of this drug. Meprobamate, mepazine and promazine on the other hand have been found superior in the mild and moderate psychoses. Combinations of drugs such as promazine and meprobamate, based on duality of action, exert a slightly stronger effect, although these, too, are not effective in controlling agitation in the acute episodes.[3,4]

As can be seen from the list of available agents, most of which have proved effective, the majority are either phenothiazine derivatives or mephenisin-like agents, the major innovations being in the synthesis of chlorpromazine analogs which produce fewer side effects. The search for drugs with more predictable activity, fewer side reactions and broader range of usefulness thus continues.

Perhaps the type of drug most sought to control the hospitalized psychotic is one that will not only calm without interfering with motor and intellectual activity but also lift the patient to a point of greater interest and productivity. With this in mind, it was decided to try a new chemical compound, chlordiazepoxide, in the control of the moderately disturbed psychotic. Newly named Librium, this drug is unrelated in structure to other tranquilizers and relaxants.[5] It is colorless, crystalline and highly soluble in water, with a molecular weight of 336.21. Its formula is:



Chlordiazepoxide

Figure 1.

Purpose

A pre-test evaluation was undertaken using 15 known psychotics of varying ages who were considered chronically ill mentally. The purpose was to establish quickly an idea as to the maximum safe dose. Medication was begun at the level of 10 mg. t.i.d. and raised in three days to 20 mg. t.i.d. Shortly thereafter, it was increased to 25 mg. t.i.d. and then to 50 mg. t.i.d. The final increase was to 100 mg. b.i.d. The top safe dose did not exceed 25 mg. t.i.d. Neurological symptomatology encountered will be discussed below.

The six months' project was begun at the East Louisiana State Hospital October 26, 1959, with 169 actively psychotic white fe-

Librium used in this study was supplied in capsules of 10, 25 and 50 mg. by Hoffman-La Roche Inc., Nutley, New Jersey.

From the East Louisiana State Hospital, Jackson, Louisiana.

males. Although the ages ranged from 20 to 79 years, about half (75) were in the fifth decade of life (Table I); 37 had been hospitalized under five years and 98 longer than ten years. The greatest length of hospital-stay was 44 years (Table II). Nearly two-thirds (110) of the patients had schizophrenia; the other mental disorders included mental deficiency, manic depressive insanity, involutional psychosis, personality and other disturbances, and chronic brain syndromes (Table III).

TABLE I

Age Tabulation

Range	Number
20 - 29	5
30 - 39	6
40 - 49	30
50 - 59	75
60 - 69	40
70 - 79	13
Total	169

TABLE II

Hospitalization in Years

Range	Number
1 - 4	37
5 - 9	34
10 - 14	32
15 - 19	23
20 - 24	21
25 - 29	14
30 - 34	5
35 - 39	2
40 - 44	1
Total	169

TABLE III

Resumé of Results

Mental Disease	Furloughed Improved	Discontinued Improved	Improved	Maintained	Worse	Total
Schizophrenia	3	8	29	44	26	110
Mental Deficiency	5	1	7	6	5	24
Chronic Brain Syndrome	1	2	4	7	1	15
Personality & Other Disturbances	1	1	0	0	1	3
Involution	0	0	1	2	2	5
Schizo Affective	1	0	0	0	0	1
Manic Depressive	1	0	3	7	0	11
Total	12	12	44	66	35	169

The entire group of 169 females had been closely evaluated while without drugs of any kind, repeated examinations given, and the chronicity of their illnesses noted. The gamut of psychotic features were present to a marked degree. Chemical restraint had been employed prior to this time with good success and Librium was put to the test to determine its relaxing ability, its power to calm, its effectiveness as a quieting agent and its usefulness as a sleep-producing drug. It was also thought wise to determine whether a small maintenance dose would be efficacious after the full effect of the drug had been produced.

The over-all purpose of the study may be most clearly expressed in outline form as an

I. EFFICIENCY AS A TRANQUILIZER *Re:*
   1. Relaxation
   2. Calmness
   3. Quietude
   4. Sedation
   5. Sleep
   6. Hangover
   7. Stupor

II. DOSAGE
   1. Minimal
   2. Maximal and tolerance to dose
   3. Cumulation and maintenance dose
   4. Side Effects

III. EFFECT ON:
   A. *Work and Other Activity*
   B. *The Physical Organism*
      1. Weight
      2. Appetite
      3. Head
      4. Circulatory System, Blood Pressure, Pulse
      5. Respiratory System
      6. Gastrointestinal System
      7. Urinary Tract
      8. Neuromuscular System
      9. Menses
      10. Sensation and Subjective Sensation
      11. Skin
   C. *Mental Symptoms*
      1. Kemptness
      2. Quietness
      3. Interest
      4. Aggressiveness
      5. Cooperativeness
      6. Speech
      7. Orientation

attempt to determine the effectiveness of Librium:

8. Apprehension
9. Attention
10. Hallucinations
11. Delusion
12. Motor Disturbances
13. Emotions

D. *Neurological Symptoms*

E. *Behavior Patterns, Personality Changes and Reality Sense*

Physical Data

Accurate charts on the physical condition of the patients were kept over the entire six months. All patients selected for the study were free from syphilis, had a negative x-ray of the chest, were ambulatory and could care for their personal hygiene. Weight variations were not remarkable and poundage did not vary in the majority from one month to another. Appetite was neither stimulated nor decreased. No pronounced nor prolonged blood pressure fluctuations were seen throughout the project. Pulse, respiration and temperature remained within the normal limits. Hemoglobin tests revealed that Librium could not be construed as affecting the hemopoietic system. Daily bowel movement charts depicted no departure from the norm, neither diarrhea nor constipation resulting. Menstrual charts recorded no dysmenorrhoea, oligomenorrhoea or menorrhagia. No seizures were reported throughout the entire series. Initially, catheterized urinalyses were run on the 169 patients and those showing pathology, from few to numerous white blood cells, were cleared within 48 hours. Re-checks validated this. None showed casts or other kidney disorder. Two patients on Librium developed kidney block and inability to urinate. On discontinuance of the medication, their kidneys again functioned normally and when the drug was resumed there was no recurrence of the pathology.

Sedative Effect

In large state hospital wards it is imperative that quiet be maintained during the evening hours and at fixed rest periods during the day. One entire ward was put on 10 mg. of Librium at h.s. but this small amount was not particularly effective. Only a few of the group were controlled and quiet.

Some patients were able to get along on 25 mg. of Librium on a twice a day basis; a third or midday dose appeared to produce drowsiness resulting in the patients preferring to lie down rather than sit up. In order to regulate their day-time activities, develop interest and stabilize ward routine, the noon 25 mg. was discontinued. On this reduced regime those able to work or take part in occupational therapy kept their usual schedules.

For the chronic cases who had been ill over extended periods of time it was found that Librium 25 mg. t.i.d. was the appropriate dose. While limiting noisiness, relieving tension and tranquilizing to a moderate degree, patients were not inhibited as to motor activity. Most were able to take part in their usual task assignments and appeared capable of carrying on as they had under the use of tranquilizing agents. There was no drowsiness the following morning and no hang-over effect. Having no A.M. tranquilizer prescribed for well over a month, there was ample opportunity to determine this accurately.

Periods of "no drug" prior to the project had shown these patients to be restless, tense, easily annoyed, irritating and annoying to others, disturbed, noisy, uncooperative and difficult to manage from the nursing and medical standpoint. When put on Sparine (promazine hydrochloride, Wyeth) for a period of some months, this drug was found to be meritorious and worthy of mention as a pace-setter for peace-on-the-ward as well as within the individual. Pacatal (mepazine, Warner-Chilcott), used for another trial period, likewise proved its worth as a mild ataractic to control semi-disturbed people. Thorazine (chlorpromazine, Smith, Klein & French) produced tranquility in these same patients in another six months period but reduced their tendency to move about; many complained that they felt log-like and lethargic.

In comparing Librium with Sparine, Pac-

atal and Thorazine over relatively similar spans of time, it was found that Librium, in amounts not over 75 mg. in 24 hours, allowed patients to release their energy and perform their work, and did not curtail their activities as did Thorazine. It was the consensus of opinion that on Librium more patients voluntarily went on the grounds, took longer walks, and were altogether more active. It was also determined that mental alertness was greater when patients were taking Librium.

Side Effects

The chief deleterious symptom produced by Librium was weakness of the lower extremities; this was seen in 19 cases. Vertigo was not a constant accompanying factor, although 10 cases complained of slight to moderate dizziness early in the project. Only on extremely large doses of the drug did ataxic behavior result and this subsided readily on reduction of dosage. One female who was allergic to at least two other tranquilizers showed a red macular dermatitis, the blush disappearing on discontinuance of the drug but re-appearing on starting it again. Because of severe itching the girl was taken off the project.

Neurological Symptoms

On one ward, in an effort to determine the dose of maximum effect and safety, the amount was pushed to as high as 200 mg. in the 24-hour period. Within the 24 to 36 hours, 15 persons reacted in a manner reflecting neurological pathology. Weakness of the lower extremities and diminution of power in hand clasp presumed some involvement of the pyramidal tract or else disturbance in the transmission of nerve impulses from the brain to the muscles of the leg and hand. Adiadochokinesis was poorly accomplished and there was incoordination of muscle movement in the finger to nose test. Muscular weakness of the lower limbs was found, at one time or another, to be present in 37 cases. Fractures occurred in two cases. Injuries of minor degree were seen in a number of individuals. Some patients fell out of bed or fell elsewhere without any external cause such as an obstacle, slippery floor or being pushed. For this reason it is deduced that muscle tone, lack of response of musculature to nerve impulse, or blocking of nerve impulse, could be assigned as the cause. Astereognosis was not disturbed. No involvement of the muscles of the eye or relaxation of musculature around the mouth was noted.

Gait and total body movements were affected by the highest doses in that patients' control over themselves was lessened. For instance, when sitting down, they would do so with a flop and their general appearance was that of falling apart. Mechanisms controlling the finer body movements were deranged; fine tremor of outstretched fingers was seen in five or six along with incoordination. Mild ataxia appeared prominently in 18 patients; of these, 11 claimed vertigo and three tinnitis. Only a few complained of headache and this was fleeting in character. No photophobia or disturbance in color sense was found. Taste, smell, sense of touch, sight and hearing were not affected. Perspiration in the palms of one or both hands was found in several people but such sudoriferous areas were also found prior to initiation of the use of Librium. It was noted that as high dosages were dropped, incoordination, tremors, weakness of the lower extremities and ataxic gait were reduced, and at a dosage of 25 mg. of Librium t.i.d. the patients showed none of these symptoms.

Mental Symptoms

Evaluation of abatement of abnormal mental traits was easily accomplished by reviewing the individuals' behavior patterns. *Appearance* was a guide to interest in self and surroundings; cleanliness and tidiness were observed in those maintained on this drug. *Quietude* and restraint of usual characteristic noisy behavior was noted in our group and was preserved throughout the project. *Cooperativeness* and adherence to ward routine as well as perseverence in tasks were prime objectives and these were observed in those maintained on the drug. *Normalcy of speech,* with neither over- nor under-productiveness, was associated with individuals well-controlled on Librium. Drowsiness was

not a concomitant symptom of the drug and mental alertness *on the level of each patient's functioning* was not impaired.

Depending upon length of hospital stay and total duration of mental illness, deteriorative processes produced poor apprehension, inability to concentrate, and inattentiveness. Librium did not reverse mental deterioration nor mask the symptoms thereof. No relief from hallucinatory experience could be prognosticated but the patients seemed to live more quietly with their delusions and hallucinations. *Emotions* in the majority of patients continued to swing without surcease but it might be stated that they did so with less agitation. No outstanding personality changes were advanced. *Reality sense* was in no way impaired by Librium but those who had already lost this sense did not regain it.

Those in the group that worsened (35 or 21 per cent) were far-advanced deteriorated and chronically ill individuals, and it was perceived that a heavier dose of tranquilizer would be required to hold in abeyance undesirable symptoms. These patients were thought to be beyond the reach of Librium, as they became violent, combative and belligerent, and since the drug could not be stepped up beyond the limit already determined, it was felt wise to discontinue them.

It is felt that Librium on the whole maintained and improved the remaining 79 per cent of the patients (134). Table III shows the over-all results by diagnostic categories. Of those begun on the project October 26, 1959, 110 were still being given the drug at the close of the study on April 26, 1960. Twelve others improved, but were sent to different wards because of factors unrelated to Librium and beyond our control; 12 were furloughed from hospital, condition improved; 66 of the 110 were maintained and 44 were definitely improved; 98 were able to leave the hospital on passes of one to five days throughout the six month period, taking no drug at all while out of the hospital.

Summary

1. In this study Librium maintained or improved mental symptoms in 134 or 79 per cent of 169 ambulatory, psychotic patients.

2. Librium produced no hangover effect and was mildly sedative in character when prescribed nocturnally.

3. Diurnal use preserved mental alertness when dosage did not exceed 75 mg. in 24 hours.

4. In some patients doses above 75 mg. in 24 hours produced vertigo, ataxia and weakness of the lower extremities, together with great drowsiness.

5. The drug does not appear to be cumulative since small maintenance doses were of no avail.

6. Librium is recommended in the armamentarium of the physician treating the mildly psychotic patient.

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REFERENCES

1. The Changing Outlook in Mental Disorders: Statistical Bulletin, Metropolitan life Insurance Company, 39:4 (May) 1958.
2. Overholser, W.: "The New Chemotherapy of Mental Illness." Gordon, H. L., ed. *Philosophical Library,* New York, 1958, p. 212.
3. Frain, M. K.: *Med. Times,* 88:317 (Mar.) 1960.
4. Frain, M. K.: *J. Louisiana State Med. Soc.,* 111: 308 (Aug.) 1959.
5. Randall, L. O.: *Dis. Nerv. Syst.,* 21:7, Supp. (Mar.) 1960.

Significant Characteristics of a Geriatric-Psychiatric Population Which Remains in Hospital

MORSE P. MANSON, PH.D.

Introduction

Many patients entering a geriatric-psychiatric service receive treatment for a limited time and then leave, never to return. Others will leave the hospital but will return later, perhaps being discharged again but returning time and again. There is a third category of patients who enter a geriatric-psychiatric hospital and never leave, remaining until they die. It is this third category of patients which is a main interest in this paper.

This study deals with all patients admitted to the Geriatric-Psychiatric Service of the Veterans Administration Hospital, Sepulveda, California, between December 1955 and March 1959 and includes 275 male patients. Of this number, 103 patients or 37% had received hospital discharges at one time or another; the remainder, 172 patients or 63% had never received a hospital discharge.

The following questions were raised and an answer sought:

1. What are some characteristics of the group which never leaves the hospital?
2. What are some characteristics of the group which leaves the hospital?
3. Are there significant differences between these groups? If so, what are they?

Method

The total group of 275 patients was divided into two sub-groups: a Non-Discharge Sub-Group and a Discharge Sub-Group. Comparisons of the two sub-groups were made on nine characteristics: (1) Race, (2) Age, (3) Marital Status, (4) Main Occupation, (5) Number of Diagnoses, (6) Kinds of Diagnoses, (7) Months Hospitalized, (8) Number of Discharges, (9) Death Rate.

Results

(1) *Race:* Both sub-groups were predominantly white. There was no significant difference between the sub-groups.

	White		Non-White	
	No.	%	No.	%
Non-Discharge Sub-Group	163	95	9	5
Discharge Sub-Group	99	96	4	4
Total	262	95	13	5

(2) *Age:* The range of ages for the Non-Discharge Sub-Group was 32-88 years; its mean age was 61.9 years. The range for the Discharge Sub-Group was 25-82; its mean age was 59.8 years. Although the discharged patients were, on the average, 3.1 years younger, this proved to be an insignificant difference.

(3) *Marital Status:* The Non-Discharge Sub-Group had a larger percentage of married men, and smaller percentages of single and divorced men than had the Discharge Sub-Group. These differences proved statistically insignificant. See Table I.

TABLE I

Marital Status

	Non-Discharge Sub-Group		Discharge Sub-Group	
	No.	%	No.	%
Single	54	31	38	39
Married	75	44	34	33
Divorced	30	17	23	22
Separated	0	0	2	2
Widowed	13	8	6	6
Total	172	100	103	100

(4) *Main Occupation:* Using the Dictionary of Occupational Titles Classification system, the main occupations of the patients were coded and classified. The three leading occupational categories for the Non-Discharge Sub-Group were "skilled," "unskilled," and "sales" work; for the Discharge Sub-Group the first three occupations were "skilled," "semi-skilled," and "protective service" work. Three occupational categories had statistical percentage differences between the two sub-groups at the .05 level of confidence. The Non-Discharge Sub-Group

From Counseling Psychology Services, Veterans Administration Hospital, Sepulveda, California.

had a significantly larger percentages of "clerical" and "building service" workers; the Discharge Sub-Group had a significantly larger percentage of "protective service" workers. See Table II.

(5) *Number of Diagnoses:* The mean number of diagnoses for the Non-Discharge Sub-Group was 2.4, that for the Discharge Sub-Group was 2.1. The difference was not significant.

(6) *Kinds of Diagnoses:* A comparative analysis of all diagnoses was made. The six leading diagnoses for each sub-group follow:

	Non-Discharge Sub-Group %	Discharge Sub-Group %
1. Psychosis	80	79
2. Chronic Brain Syndrome	59	51
3. Cardiovascular Disease	22	22
4. Incompetent	17	12
5. Tuberculosis—Inactive	15	9
6. Psychoneurosis	6	9

Only one significant difference was found. The Non-Discharge Sub-Group had a significantly higher percentage of patients with "tuberculosis-inactive" than did the Discharge Sub-Group. This difference was significant at the .01 level of confidence. See Table III.

TABLE II
Main Occupations

Occupations	Non-Discharge Sub-Group No.	%	Discharge Sub-Group No.	%
Professional	8	5	8	8
Sub-Professional	4	2	4	4
Managerial	5	3	2	2
Clerical*	14	8	3	3
Sales	16	9	5	5
Domestic	1	1	1	1
Personal Service	4	2	2	2
Protective Service*	5	3	9	9
Building Service*	8	5	1	1
Agricultural	11	6	9	8
Fishery	0	0	0	0
Forestry	0	0	1	1
Skilled	41	24	27	26
Semi-skilled	7	4	10	10
Unskilled	18	11	7	7
Unknown	30	17	14	13
Total	172	100	103	100

*Percentage difference is significant at the .05 level.

TABLE III
Kinds of Diagnoses

Diagnoses	Non-Discharge Sub-Group No.	%	Discharge Sub-Group No.	%
Psychosis	138	80	81	79
Incompetent	29	17	12	12
Senile Deterioration	11	6	4	4
Psychoneurosis	10	6	9	9
Mental Deficiency	2	1	1	1
Chronic Brain Syndrome	102	59	52	51
Epilepsy	6	4	2	2
Parkinson's Disease	1	1	4	4
Cardiovascular Disease	38	22	23	22
Tuberculosis—Inactive*	25	15	4	4
Pulmonary Disease	6	4	5	5
Gastrointestinal Disease	4	2	3	3
Orthopedic Disorders	16	9	6	6
Arthritic Disease	6	4	1	1
Dermatologic Disease	4	2	0	0
Sensory Disorders	3	2	4	4
Cancer	5	3	1	1
Miscellaneous	15	9	6	6

*Percentage difference between Non-Discharge and Discharge Sub-Groups is statistically significant at the .01 level of confidence.

(7) *Months Hospitalized:* The mean number of months hospitalized for the Non-Discharge Sub-Group was 26.0 months; for the Discharge Sub-Group it was 18.9 months. The Difference of 7.1 months was significant at the .01 level.

(8) *Numbers of Discharges:* The Non-Discharge Sub-Group had received no discharges, while the Discharge Sub-Group had received, on the average, 1.3 hospital discharges. The difference was significant at the .01 level.

(9) *Death Rate:* The Non-Discharge Sub-Group included 36 patients who died during the 39 months of the study. This was 21% of this group. For the Discharge Sub-Group, a follow-up study by Manson and Engquist[1] resulted in 56 responses and revealed that over a perior of 44 months five patients had died. Using this group of 56—rather than the group of 103—the percentage of deaths for the Discharge Sub-Group was 9%. The difference was significant at the .01 level.

Discussion

No significant differences between the Non-Discharge Sub-Group and the Discharge

Sub-Group were found relative to race, age, marital status, and numbers of discharge.

Three significant differences in main occupations were noted. These indicate that clerical workers and janitors or maintenance workers have considerably more difficulty leaving a geriatric-psychiatric hospital than do other workers. It also appears that men who worked as guards, policemen or were in the military services have more chance to leave than do other workers.

It was surprising to find only one significant diagnostic category. Apparently a history of "tuberculosis" markedly reduces the probabilities of a geriatric-psychiatric patient leaving a hospital. However, a diagnosis of "psychosis" or "chronic brain syndrome" has little effect on whether a patient stays or leaves a hospital.

It was expected that the Non-Discharge Sub-Group would stay longer in the hospital, and this was verified. This Sub-Group stayed at least 7.1 months longer than did the Sub-Group receiving discharges.

The one real difference noted in the diagnostic categories points to the conclusion that diagnostic categories have little predictive value as to which patients leave or stay in the hospital. However, the marked difference in death rate contradicts this conclusion. Apparently, the Non-Discharge Sub-Group, although not greatly different from the Discharge Sub-Group in numbers of diagnoses or kinds of diagnoses, must have been a considerably more pathological group, and hence had more deaths.

Summary

1. A group of 172 male geriatric-psychiatric patients who had never received a hospital discharge was compared with a group of 103 male geriatric-psychiatric patients who had received previous hospital discharge.

2. Comparisons were made on race, age, marital status, main occupations, numbers of diagnoses, kinds of diagnoses, hospital time, numbers of discharges, and death rate.

3. Findings suggest the two sub-groups have much in common and few real differences.

REFERENCE

1. Morse P. Manson, Ph.D., and Carlton L. Engquist: Post-Hospital Adjustments of a Geriatric-Psychiatric Group. Unpublished 1960.

SEVENTH ANNUAL MEETING ACADEMY OF PSYCHOSOMATIC MEDICINE

The Academy of Psychosomatic Medicine will hold its Seventh Annual Meeting at the Benjamin Franklin Hotel in Philadelphia, Pa., from October 13th to 15th, 1960. In keeping with the general theme, "An Inter-Disciplinary Approach to the Emotional Problems Encountered in Medical Practice," participants will include generalists and specialists in clinical medicine, cardiology, allergy, obstetrics and gynecology, plastic surgery and neurosurgery, as well as psychiatrists, psychoanalysts, and researchers in psychopharmacology. The three day program includes panels and symposia on: Interview Techniques, Drugs and Research, Organic Aspects of Psychiatry, Group Therapy, Psychopharmacology, Drugs and Psychotherapy, Hypnosis, and a variety of other topics. For further information, contact Bertram B. Moss, M.D., Secretary, 55 E. Washington, Suite 1035, Chicago 2, Illinois.

Psychological Factors in the Decline of an Industry

EDMUND BERGLER, M.D.

It is well known that necessity alone cannot account for the existence, prosperity or size of an industry. The psychologically propelled vitamin craze, for example, promoted the sale of citrus fruits to new heights. The popularity of perfumes rests partly on the fact that they provide an inner defense against (and an acceptable substitute for) the infantile predilection for "disagreeable" odors. Sometimes psychological and practical factors combine to weaken or even sweep away an industry, as the boned corset has virtually disappeared under the double onslaught of woven elastic and woman's psychological rejection of painful constriction. Many other examples may be adduced.

In our day and under our noses a whole industry is vanishing—unsung, almost unnoticed. I have in mind the millinery industry. It is true that the creators of hat styles and the hat workers' union complain bitterly and indomitably about the "foolishness" of women who go without hats. A casual look around in any well-frequented street shows why these complaints are so persistent. Most women today are hatless, and those who cover their heads tend to prefer a form of bandanna.

Who or what killed the female hat? The malefactor is a quartet of psychological reasons.

1. *The Lady Without a Hat.* In the past no "lady" would ever appear in public without a hat; it was an essential part of the uniform which indicated her position as "a lady." Only "peasant women," domestics, "uncultured" could afford to venture into the street hatless. Today this screening process seems to have been reversed, and the "lady" dispenses with the hat. Sociologists may naively assume that this fact mirrors the trend towards greater democratization, but this is dubious. It is more likely that the rebellion against the hat is part and parcel of the general feminine trend towards greater ease (meaning less constriction) in dress generally. Fashion is now paying the penalty for its cruelty towards women. For centuries fashion used women as if they were puppets, constricting their bodies and disregarding their physical comfort.

2. *Accent on Youth.* The "dignity of age," once awarded as a sort of consolation prize for the appearance of gray hair in women, is now a dead letter. Its successor is the pursuit of eternal youth. This is not surprising in a society given to early marriage; many women of 37 today are grandmothers. Moreover, medical and cosmetic progress enables middle-aged women to look younger than their years. Today a woman may reach the ripe age of 70 without psychologically having to acknowledge her age in her external appearance. "Hair colorists," cosmeticians and anti-wrinkle specialists (one has only to think of the billion-dollar cosmetics industry) have contributed to this end.

3. *Well-Groomed Hair and Beauty Parlor as Hat-Killers.* The beauty parlor gave the hat its *coup de grace.* It was in the beauty parlor that women discovered a new feature for public display: their hair. The weekly visit to the hairdresser, the high cost of permanents, hair dyes, hair sets meant an investment (and an effect) too important to be hidden. After all, everybody wants something to show for their money. Moreover, many hats interfere with the coiffure. Women have therefore discarded the hat and now emphasize the coiffure. This choice was made easier by the hat's inherent faults: it is expensive, it frequently does not fit, it often makes its wearer look ridiculous.

4. *The Crime of the Homosexual Designers.* In "Fashion and the Unconscious," published in 1953, I pointed out that women are dressed by their worst enemies: the homosexual Continental designers still rule fashion to a great extent. Homosexuals are inwardly mortally afraid of women; in their frantic flight from that danger they run to "another continent," man. As inner defense against their fears, they hate and reject

women. If they are employed in the fashion industry, they give vent to their pseudo-aggression by designing clothes that are uncomfortable, restricting or caricaturistic; often these clothes deprive women of all female characteristics. A survey of fashions of the last decades proves the point:

The hobble skirt fashionable at the beginning of the century made it difficult, if not impossible, to walk. Today the same difficulty is revived in the modern hobble skirt, the so-called hemband, which impedes locomotion by being narrow at the knee instead of at the ankle. (This relaxation of constriction from ankle to knee is not very impressive progress for half a century.) Spike heels make walking no less hazardous an undertaking. The bustle, combined with a tight corset made each breath a project and gave its wearers a ridiculous look, like a horse with a tail. The crinoline turned women into barrels; the flapper style turned them into boys. The recent sack also deprived women of feminine characteristics, eliminating from view all female organs distasteful (meaning fright-inspiring) to the homosexual. This sampling could be enlarged.

The unconscious ill will of homosexual designers, which makes women into caricatures, is aided and abetted by the psychic masochism of female "fashion apes," who would wear anything "to be fashionable." A patient told me of meeting a famous artist at a party a few years ago, when the tight waist (an exquisite method of torture!) was in vogue. The artist had just returned from the Paris collections, and he looked her over critically. "Your belt is all wrong," he said, drawing it tighter. "I can't breathe!" she objected. "You are not supposed to," he replied.

Homosexual designers of hats on the Continent have had their fun, just as the fashion designers proper have. One has only to remember the monstrosities that "adorned" women's heads during the time when a hat had to be a miniature garden or flower bed. These burdens were so great (actually, or by innuendo) that one cannot escape the impression that these homosexual hat designers were thinking of a peasant woman carrying a heavy load on her head.

The shape of the human head is dangerous to tamper with. In clothing the least ridiculous effects are achieved when direct outlines are followed. The "cute little hat" so many men stress retrospectively in recollecting their past seems to have pleased them: it did not detract from the face, but outlined it. An added advantage is that it did not *frighten* them. One should not lose sight of the fact that the great "he-man" is inwardly *also* scared of woman. It seems that this inner fear accounts for the ease with which some men laugh at some types of women's hats. Their mirth is but a defense.

In recent years, Continental milliners have tried to force the big, heavy hat on women. They went about it as if women still unconditionally followed the dictates of hat fashions. That means that they don't even understand what hit them; they were totally unsuccessful in forcing women to obey.

The over-sized (or towering) hat, especially when worn by a tall woman, inwardly intimidates the poor he-man. It makes a small woman look absurd. Worn by either a tall or a short woman, it signalizes a victory for the malicious homosexual designer whose purpose is to uglify or damage women.

Why is the big hat so unbecoming and laughter-provoking? It seems that the big hat duplicates the shoulder line, thus invoking the Bergsonian law explained in "Le Rire" in 1901. Bergson's formula for laughter,, "something mechanical encrusted on the living," is incomplete, but it applies to this specific case. Bergson believed a comic impression always resulted when a human being performed the motions of an inanimate machine. Bergson connected the comic of imitation with a problem posed by Blaise Pascal (1623-1662) in his "Pensees": why do we laugh when comparing two similar faces but would not laugh at either face seen separately? Exact repetitions or complete similarities ring false, Bergson declared, and arouse the suspicion that some mechanism is at work in the background. If two faces are too much alike, the impression is of two heads cast in the same mold, two impressions of the same soul, two positives from the same negative—in other words, of a

manufacturing process of one kind or another. This turning of life into a mechanical process is the cause of laughter in this case, claims Bergson; it might be called degrading humanity by making it mechanical or inanimate.

The semi-collapse of the millinery industry is an example of the importance of psychological factors for people who have never heard of, or have nothing but contempt for psychological-psychiatric facts. The irony is that the process is by no means finished. When the girl on the street *believes* what today she only *knows* intellectually—that ladies don't wear hats—the full collapse of the millinery business probably will follow when the slogan of "status seeking" becomes inapplicable.

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Hydroxyzine (Atarax) in the Treatment of Non-Institutionalized Psychotics

E. Louis Reder, M.D.

Though electroshock therapy (EST) has been the treatment of choice in affective psychoses, this procedure presents difficulties for the patient, his family, and in private practice, for the psychiatrist. In some instances, complaints attendant upon EST are quite as incapacitating to the patient as the psychosis itself. There are, in addition, some patients whose physical status makes them ineligible for this therapy. Or, the patient's family, for various non-medical reasons, may refuse to consent to electroshock therapy. Accordingly, the search among the newer drugs has been for compounds which will provide control and safety in affective psychoses, ,the aim being either to replace EST or reduce the number of treatments required and the after-effects.

For patients in extreme agitation and depression, restraints and hospitalization have been necessary. Higher doses of tranquilizers than customarily used for office outpatients have with varying degrees of success been administered, subject to close supervision and observation by nursing personnel and with frequent laboratory studies. The proved value of most of these agents is well known as is their potential toxicity.

In contradistinction to tranquilizers such as meprobamate and those in the phenothiazine group, hydroxyzine has been shown to present a very low order of toxicity along with a high therapeutic index. Despite the fact that this drug has been in wide use for almost five years, in more than a quarter of a billion patient doses, the world literature does not report a single instance of serious toxicity ascribed to it, even though dosages as high as 3000 mg. daily have been reported.[2]

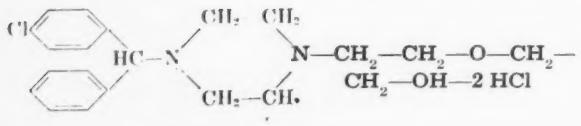
The present writer thus determined that trial of this agent in moderate to high dosages was warranted in patients with affective psychoses for whom either prolonged hospitalization or extensive electroshock therapy was not feasible. Family supervision of the patient, of course, was a requirement. It was further decided to use this agent as a follow-up to a short course of electroshock therapy, to determine whether hydroxyzine would appreciably reduce the extent of this treatment needed. The purpose of this paper is to review the pharmacology of hydroxyzine and to report on the methods and results of the clinical study.

Pharmacologic Aspects of Hydroxyzine[3-5]

Hydroxyzine is designated chemically as 1 - (p-chlorobenzhydryl)-4-2-(2-hydroxyethoxy)-ethyl diethylenediamine dihydrochloride. Its structural formula is shown as

The compound, hydroxyzine used in this study has been supplied as Atarax by J. B. Roerig and Company, Division, Chas. Pfizer & Co., Inc.

From Greenpoint Hospital, Evangelical Deaconess Hospital, Bethany Deaconess Hospital, and Menorah Home & Hospital, New York City.



Hydroxyzine hydrochloride

Figure 1.

Hydroxyzine hydrochloride suppresses some of the hypothalamic nuclei and extends its effects peripherally in the sympathetic portion of the autonomic nervous system where it depolarizes nervous and muscle fibers. Except in extremely high doses it has no apparent effect on the cerebral, thalamic, or spinal cord areas. There is also evidence that part of its activity is caused by a depressant action on the reticular formation. Hydroxyzine inhibits the somatic effects of excitatory drugs such as epinephrine, dextro-amphetamine, mescaline, and lysergic acid.

Experimentally, hydrozyzine decreases motor activity by a direct relaxing effect on muscles. Excitable tissues are depolarized. The local anesthetic effect is equal or greater than that of procaine. The spinal cord and higher centers of the central nervous system are not depressed by the drug and may even show increased activity at very high doses. The hypothalamic and peripheral depressant effects of hydroxyzine in the absence of central depression explain its effect upon the response of experimental animals to cortical stimulants and hallucinatory drugs. Electroencephalographic studies have shown that the effects of excitatory drugs are diminished very little, if any, whereas the behavior of the animals may be greatly altered. In other words, the electrical impulses are not diminished but the animals appear outwardly calm.

Clinically, hydroxyzine hydrochloride reduces muscle tension without interfering with equilibrium or cerebral activity. Normal and abnormal electroencephalographic tracings are altered very little. Although the somatic effects of dextero-amphetamine are inhibited, cerebral stimulation is still evident. Volunteer subjects given lysergic acid showed no electroencephalographic changes when hydroxyzine was administered, nor was the skin flush altered; however, the behavioral aspects were diminished and the subjects appeared less confused.

Materials and Methods

In this study 35 psychotic patients (21 females and 14 males), ranging in age from 21 to 82 years, were treated with hydroxyzine. The diagnostic categories were affective psychoses (28 patients); pseudo neurotic schizophrenia (5 patients); senile psychosis (1 patient); and obsessive compulsive (1 patient). Among the patients with affective psychoses were cases of manic depression (manic or agitated) and postpartum depression.

It must be emphasized that almost all of these patients had been treated with various medications by other physicians before consulting the present writer; some had had earlier treatment with electroshock. When first seen and on the basis of prior history, all these patients showed symptomatic indications for EST, preceding physical evaluation.

Cases may be classified in two series. Group I consisted of 29 non-institutionalized psychotic patients seen in office practice who, though excellent candidates for EST, refused this treatment on a voluntary basis and were instead given a course of therapy with hydroxyzine hydrochloride. Group II consisted of six psychotic patients who were so severely affected that an emergency course of electrotherapy was deemed necessary. EST was given on successive days for three to five days, before instituting therapy with hydroxyzine. During the emergency period, these patients were institutionalized, usually for a week.

In both series (with or without EST), when medication was begun, a common procedure was to give 800 mg. of hydroxyzine per day in divided doses every three hours around the clock. These persons, it must be recognized, had generally not slept well for many days preceding treatment. Sleep and rapid control of symptoms were much needed. After three or four days, depending

on the response of the patient and the nature of the complaint, emergency high dosages were gradually reduced to as little as 10 mg. b.i.d. (in some few cases) over a period of weeks. All were carefully supervised by the writer, the patient's family, or hospital personnel (for those few who were briefly institutionalized) and almost daily contact was maintained by visits or phone calls at any hour of the day or night.

Results

In Group I, 29 patients given hydroxyzine in place of electroshock therapy, results obtained in affective psychoses (22 patients with manic or agitated depressions) were uniformly excellent. All of these patients obtained remission of symptoms and were able to return to their regular work or home patterns of life.

Of the remaining seven patients in Group I, good results were obtained in a single patient with senile psychosis. This patient was thereafter able to be maintained in a nursing home which had not been possible before. With hydroxyzine therapy excellent results also occurred in an obsessive compulsive patient and he was able to return to work. There were five other patients in this group who were diagnosed as pseudoneurotic schizophrenics. With hydroxyzine, three of these persons obtained excellent relief and were able to return either to their home or job responsibilities; failures occurred in two other patients who were then committed to state hospitals.

Typical case reports in Group I are these:

A. S., a female, age 68, widow with three children. Three months prior to first visit had undergone operation for removal of gall bladder. Was severely depressed. Could not sleep, lost weight because of nausea, vomiting and refusal to eat. Was considered a poor risk for shock therapy. Required intravenous supportive therapy. Placed on Atarax, 100 mg. every four hours. She slept better, began to eat and made an excellent clinical recovery. One of the features of her illness was the refusal to leave the house, let alone travel. As a result of response to Atarax (which she is now taking in doses of 25 mg. three times a day) she has been able to travel to the airport and go by plane to Cuba to live with her son who owns a plantation there.

M. T., a female, age 45, single, employed as a clerk. *Diagnosis:* Manic depressive reaction. *Past History:* Eight years before she had a hysterectomy and then a course of electroshock therapy. Did well for five or six months and then every six months thereafter up through the middle of 1958, required a course of two shock treatments to keep her "normal," by which I mean able to eat and sleep properly and continue working. At one time I felt that this would be a permanent procedure for the rest of her life. At the end of the six months period, when the patient again began to "relapse," she was placed on Atarax, 100 mg. every three hours for two days and then three times a day. At the end of a week she was back to her usual self and no difference was noted in the type of improvement from the Atarax than previously noted from the electroshock.

H. T., a male, age 53, married with two children was an insurance broker. This man has been under my care for over eight years. He was originally turned over to me "in disgust" by an internist because of chronic alcoholism. He has been hospitalized on many occasions because of delirium tremens, alcoholic psychosis, alcoholic hallucinosis and alcoholic peripheral neuritis. The basic diagnosis was established as a manic depressive psychosis with frequently recurring attacks of agitated depression for which the patient would take alcohol as a cure. Three months ago he had neurological signs of a peripheral neuritis with a partial paralysis of both lower extremities and what appeared to be a covering Korsakoff's psychosis. Fortunately, he responded to vigorous medical treatment and the organic signs were reversed. The deteriorative mental signs were also reversed but of course the underlying psychotic depression was untouched. He was placed on Atarax, 100 mg. four times a day. The results were surprising. He was very relaxed, slept well and gained 18 pounds in weight. As of now, he is on a 100 mg. three times a day, without drowsiness, mentally clear and alert and able to run his insurance brokerage office successfully. He may continue on this high dosage indefinitely since there are no side effects whatsoever.

In Group II, six patients were given 3 to 5 emergency EST treatments on successive days while temporarily institutionalized, before starting hydroxyzine therapy. Four patients who were manic depressives obtained excellent relief and were able to return to society. Two patients in postpartum depression were failures; these patients required further hospitalization and treatment. Typical case reports in Group II are these:

M. E., a female, aged 54, married, with two children. Treated by physician for gastrointestinal complaints without success. About three or four weeks prior to first interview, she developed agi-

tated depression. Received three electric shock treatments as an emergency procedure. Thereafter, placd on Atarax, 100 mg. three times a day for one week. Discharged as "cured" with no further somatic complaints.

K. H., male, age 64, married, two children. Occupation, baker. Developed a severe agitated depression two weeks prior to first contact. Attempted suicide on two occasions. Given two electric shock treatments. Then placed on Atarax, 100 mg., four times a day for two weeks. Not drowsy and remained calm and relaxed. Changed to 25 mg. three times a day and is doing well. Can go back to work but is going to continue on sick leave for one month and go to Florida on vacation.

Discussion

It is not proposed that ataractic substances, with or without adjunctive electrotherapy, ,may be the panacea for permanently curing psychoses. Even though successful results were obtained with hydroxyzine, granting the patient relief and the opportunity to live and work more normally, it is possible that regressions and relapses may occur. Permanent control of exacerbations might never be obtained in some patients, while others might hope for lasting relief only following prolonged psychotherapy.

Electroshock therapy is necessarily costly, particularly where this treatment is not given in the office of the practitioner, and the number of physicians who are willing to provide EST in their offices is diminishing. Hospitalization is likewise expensive and many of the health insurance plans contribute only a portion of the cost of electrotherapy or temporary hospital stay. And, again, many patients can not or may not be given EST.

In view of these facts, the over-all 89 per cent successful result obtained with hydroxyzine becomes even more meaningful. Without EST (Group I), 93 per cent successful results were obtained; with a short course of EST (Group II), 66 per cent successful results occurred. Before the advent of tranquilizers, it must again be stressed that these patients would have been prime candidates for EST. With hydroxyzine, recourse to EST was avoided or reduced in a number of treatments. In 27 of 29 patients who might otherwise have been given EST it was not used at all and with 3 to 5 electrotreatments plus hydroxyzine, control was obtained in 4 of 6 patients who might have required prolonged EST and hospitalization.

Conclusion

In view of these findings, it is concluded that the use of hydroxyzine hydrochloride in the method described can reduce materially the need for EST in affective psychoses. It is further believed that hydroxyzine therapy can appreciably reduce the total number of EST treatments which may be required in these patients. The author believes that affective psychoses may be treated specifically with hydroxyzine hydrochloride.

REFERENCES

1. Lapolla, A.: High Dosages of Hydroxyzine in the Treatment of Institutionalized Mental Patients. To be published.
2. Lipton, M. I.: High Dosage of Hydroxyzine in Out-patient Treatment of Severe Neuroses and Psychoses. To be published.
3. Hutcheon, D. E., Scriabine, A., et al.: Pharmacology of Hydroxyzine, a New Tranquilizing Drug. Read at Am. Soc. Pharmacol. & Exper. Therap., Indiana (Nov. 8-10), 1956.
4. Hutcheon, D. E., et al.: Cardiovascular Action of Hydroxyzine. *J. Pharmacol. & Exper. Therap.*, 118:451 (Dec.) 1956.
5. Sherrod, T. R.: Antispasmodic Properties of Hydroxyzine (Atarax). *Toxicol. Appl. Pharmacol.*, 1:162 (March) 1959.
6. Farah, Luis: Preliminary Study of the Use of Hydroxyzine in Psychosomatic Affections. *Internat. Rec. Med. & G.P. Clinics*, 169:397 (June) 1956.
7. Loeb, C.: Lysergic Acid Diethylamide Effects Modified by Hydroxyzine Hydrochloride. *Confinia neurol.*, 19:40-51 (Jan.) 1959.
8. Levis, S., et al.: A Pharmacological Study of Hydroxyzine (1) or U.C.B. 492, a Bisubstitute Derivative of Piperazine. *Arch. Internat. Pharmaco et Therap.*, CIX, No. 1-2, pp. 127-192.

Fluphenazine Treatment in a Receiving Hospital Setting

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Fluphenazine dihydrochloride is a fluorinated phenothiazine derivative of the piperazine type. Theoretical considerations[1] as well as clinical[2,3] and laboratory findings[4] indicate that fluphenazine is an ataractic agent characterized by: (1) a relatively low dosage range (usually less than 15 mg. per day); (2) an appreciable incidence of extrapyramidal side effects; (3) a wide margin of systemic safety; and (4) usefulness in psychotic illness with minimal sedative action.

The present study was designed to test the effectiveness of fluphenazine in the treatment of acute psychiatric conditions. Accordingly, a group of patients was given the medication shortly after admission to a receiving hospital and the response was noted after one week of treatment.

Method

A total of 54 male and female ward patients at Kings County Hospital were treated with fluphenazine. In addition, a comparison group of 19 female patients was treated with a placebo. As seen in Table I, the age range of the patients studied was wide and a variety of diagnoses were included. Within the schizophrenic category were included patients of all the subtypes. Generally excluded from the study were alcoholics and patients with systemic illness. Furthermore, since only oral medication was used, patients requiring parenteral medication were also eliminated from study.

The setting of the present study is that of a psychiatric receiving hospital. The patients are generally brought to the hospital directly from the community. Within the hospital, the patients undergo an observation period with some limited treatment and a definitive disposition after a week or two in the hospital. A patient in need of further inpatient treatment is committed to a state hospital. The patients in the present study are representative of the type of admission seen in this receiving hospital, although, as mentioned, the sample is neither consecutive nor random.

TABLE I

Patient Characteristics

	Fluphenazine		Placebo
AGE	Male	Female	Female
Mean	35.0 yrs.	39.6 yrs.	36.9 yrs.
Range	19–66	20–83	23–68
DIAGNOSIS			
Schizophrenic reaction	17	27	17
Involutional reaction	3	1	1
Alcoholism	2	–	1
Chronic brain syndrome	1	3	–
Total	23	31	19

Drug treatment was usually begun within three days of admission. During the predrug period, baseline observations were made and medication was withheld. Conventional sedatives such as paraldehyde and chloral hydrate were given during this preliminary period if the clinical situation seemed to demand it. The actual drug treatment period usually lasted seven days. Fluphenazine was administered on a flexible dosage schedule in capsule form. The treating psychiatrist gauged the dosage by the clinical condition. Placebo was administered to the comparison group in identical capsule form on a similar flexible dosage schedule. The treating psychiatrist was aware of the contents of the capsules.

In using fluphenazine, the usual practice was for the psychiatrist to start the patient on a daily dosage below 5 mg. and increase it until a satisfactory response was noted. The maximum dosages for the individual patient ranged from 2 to 20 mg. per day. The mean for the maximum dosage used was 8.75 mg. The general tendencies were for the doctors to arrive at a maximum dosage 5 or 6 mg. (19 cases) or 10 mg. (16 cases).

Daily observations were made throughout

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the hospital stay. Blood pressure was taken daily. Total white counts and liver studies were done at about three-day intervals. In addition to the usual progress note record, the treating psychiatrist attempted to quantify his judgment of change through two methods. One method was a global rating on a five-point scale made at the end of the treatment period. The scale ranged from "much worse" (—2) through "much improved" (+2) with the midpoint (0) representing no change. The other quantitative method was the Target Symptom Rating Scale (TSRS), composed of 16 items pertaining to the range of clinical psychiatric observations. Such features as "manifest anxiety" or "paranoid symptoms" were rated on a four-point scale of "none," "mild," "moderate," or "severe." In addition to the ratings, the psychiatrist designated one of the items for each patient as the "target symptom," that is, a prominent area of the psychopathology toward which his treatment was directed. The TSRS was completed at the beginning and end of the treatment period.

Findings

Our findings relating to clinical response may be grouped under three headings, based on the evaluative techniques used: (1) global changes, (2) target symptom changes, and (3) individual TSRS item changes. The latter two areas are based on an analysis of the TSRS scores, the difference being taken between the baseline and post-treatment ratings.

The number of patients involved in the different findings will vary since information was at times incomplete and various clinical situations arose which invalidated individual case studies in different ways. Examples of such situations are the introduction of other drugs into the treatment or accidental failure to administer the prescribed agent.

Global Changes. The over-all clinical response pattern of the fluphenazine-treated patients was compared to the placebo series. For purposes of the analysis, the degree of improvement (+1, +2) or worsening (—1, —2) has been ignored and the patients designated as 'worse," "no change," or "improved." As shown in Table II, the fluphenazine-treated patients fared much better than the placebo-treated ones in the doctor's global judgment. The fluphenazine group showed an improvement rate of 66.7% as opposed to the placebo group with 36.8%. By the chi-square method the difference was significant at approximately the .05% level.

Global changes were compared for various age groups and no remarkable variations were seen. In Table II is shown the improvement rates according to age range when the distribution by age is divided into three groups approximately equal in size.

The next consideration was the possible relationship of global change and dosage schedule utilized. The patients were divided according to whether they were above or below the mean maximum dosage per day and the improvement rates of the two groups compared. As shown in Table IV, the improvement rate for the lower dosage group was 72.0% as opposed to 60.9% for the higher dosage group. Although the findings show no statistically significant trend, they do suggest that increased dosage is not accompanied by increased efficacy of drug action in this population and setting.

TABLE II

Global Clinical Change with Placebo and Fluphenazine Treatment

GLOBAL CLINICAL CHANGE

Treatment Received	Worse No.	Worse %	No Change No.	No Change %	Improved No.	Improved %	Total No.	Total %
FLUPHENAZINE								
Male	–	–	3	16.7	15	83.3	18	100.0
Female	3	10.0	10	33.3	17	56.7	30	100.0
Total	3	6.2	13	27.1	32	66.7	48	100.0
PLACEBO								
Female	4	21.1	8	42.1	7	36.8	19	100.0

TABLE III

Fluphenazine Treatment Response According to Age

GLOBAL CLINICAL CHANGE

AGE RANGE	Unimproved	Improved	Total
19–30	6	10	16
31–39	4	11	15
40–83	5	11	16
Total	15	32	47

Target Symptom Changes. For each patient studied, one prominent area of the psychopathology was designated as a target symptom. The target symptom represented the psychiatrist's value judgment as to what aspect of the psychopathology was most important in the psychotic picture as well as what aspect might be most benefited by the treatment. The target symptoms in the present series were grouped into five categories: depression, agitation, confusion, anxiety, and paranoid symptoms. Because of the paucity of cases within the categories, conclusions regarding the effects of fluphenazine on target symptoms must be made cautiously.

Despite the small number of cases, three of the target symptom groups, as seen in Table V, presented suggestive trends: depression, anxiety, and paranoid symptoms. Among the depression group, 16 out of 20, or 80.0%, showed improvement with fluphenazine while none out of the four placebo cases improved. Among the paranoid cases, seven out of 10, or 70%, improved with fluphenazine as opposed to two out of five, or 40%, with placebo. The anxiety group is of interest because of the negative result obtained. With fluphenazine the improvement rate among the anxiety cases was 31.7% (5 out of 12 cases) while with the placebo 57.1% (4 out of 7 cases) improved.

Because of the impressive improvement rate, the depression group was considered in some detail. Within this group were included a range of symptoms such as psychomotor retardation, severe apathy, and depressed mood. Also in the group were two patients with catatonic features. In order to study the possible relationship of diagnosis and response to fluphenazine, the twenty depressed patients were classified according to whether or not they were schizophrenic. Although our sample is heavily weighted for schizophrenic diagnoses in general (Table I), the results with the depression group show an interesting trend. As seen in Table VI the schizophrenic depressed patients improved in 14 out of 15 cases while the nonschizophrenic depressions improved in only two out of five cases. Another factor considered for the depression group was sex. As seen in Table VII, improvement rates were substantial for both male and female patients, although the males showed a much higher rate of improvement.

Individual TSRS Item Changes. The 16 item TSRS was filled out by the psychiatrist at the beginning and end of the treatment period. The TSRS scores were studied for change trends as a group regardless of the

TABLE IV

Fluphenazine Treatment Response According to Maximum Dosage Used

GLOBAL CLINICAL CHANGE

Dosage Range	Unimproved		Improved		Total	
(mg./day)	No.	%	No.	%	No.	%
2–7.5	7	28.0	18	72.0	25	100.0
9–20	9	39.1	14	60.9	23	100.0
Total	16	33.3	32	66.7	48	100.0

TABLE V

Target Symptom Changes

Target Symptom	Fluphenazine			Placebo		
	Unimproved	Improved	Total	Unimproved	Improved	Total
Depression	4	16	20	4	–	4
Agitation	1	3	4	2	–	2
Confusion	1	1	2	–	1	1
Anxiety	7	5	12	3	4	7
Paranoia	3	7	10	3	2	5

TABLE VI

Fluphenazine Response of Depression Group According to Diagnosis

GLOBAL CLINICAL CHANGE

Diagnosis	Unimproved	Improved	Total
Schizophrenic	1	14	15
Nonschizophrenic	3	2	5
Total	4	16	20

TABLE VII

Fluphenazine Response of Depression Group According to Sex

CLINICAL CHANGE

Sex	Unimproved	Improved	Total
Male	2	11	13
Female	2	5	7
Total	4	16	20

individual's baseline condition or target symptom. In doing this the difference scores between the beginning and end ratings were compared for the two treatment groups, fluphenazine and placebo. The means of the differences for the two groups are shown in Table VIII. These over-all scores represent group trends when the baseline characteristics of the patients are ignored. This is in contrast to the target symptom ratings which focus on predominant patient characteristics. As shown in Table VIII some change in a positive direction was the rule for both placebo and fluphenazine cases; and in most cases the gain with fluphenazine and placebo difference scores by Student's t test was statistically significant below the .01 level for four items (hallucinations, manifest anxiety, unexplained anxiety, and phobias) and below the .05 level for one item (agitation). These findings are of particular interest in view of the fact that the findings for the target symptoms of anxiety and agitation were inconclusive.

Side Effects

A range of side effects was seen in the present study. By far the most prominent side effect was extrapyramidal symptomatology, affecting 13 patients, or 24.0%. A lowering of blood pressure was associated with some symptoms in nine patients, or 16.7%. The hypotensive symptoms were mild, the severest being in one patient who blacked out a few times on standing quickly. Several patients noted drowsiness at the beginning of treatment, which usually cleared within two days of continued treatment. One patient developed a papular pruritic rash of the trunk after two days of treatment, which gradually faded during a week of continued fluphenazine medication.

TABLE VIII

Mean Rating Scale Differences for Fluphenazine and Placebo Treatment Groups

Rating Scale Item	Fluphenazine Mean	Fluphenazine No.	Placebo Mean	Placebo No.	t Value
Hallucinations	.50	22	.06	16	3.49
Agitation	.65	23	.12	17	2.39
Manifest anxiety	.78	23	.06	17	2.75
Unexplained anxiety	.85	20	.06	17	3.75
Somatic anxiety signs	.55	20	.23	17	N.S.
Phobias	.65	20	.06	17	2.85
Vague fears	.40	20	.12	17	N.S.
Paranoia	.52	23	.53	17	N.S.
Thought disorder	.22	23	.23	17	N.S.
Depression	.18	22	.18	17	N.S.
Apathy	.39	23	.06	17	N.S.
Treatment interest	.13	23	.23	17	N.S.
Denial of illness	.05	22	.06	17	N.S.
Body preoccupations	.45	20	.12	17	N.S.
Suicidal ideas	.25	20	.23	17	N.S.
Hostile impulses	.16	19	.06	16	N.S.

For 2 df, P=.05, when t=1.96
For 2 df, P=.01, when t=2.58

The extrapyramidal symptoms seen in this group of patients were similar to those described generally.[1] They fell into two main types: parkinsonian and dystonic manifestations. The dystonic symptoms consisted of writhing movements or sensations of stiffness and most commonly involved axial musculature: neck, tongue, throat, back, scalp. The dystonic symptoms could often be seen as isolated manifestations at their inception —for example, cramps involving only the back of the neck. One patient complained of "kidney pain" which proved to be stiffness on one side of the lumbosacral musculature. No attempt was made to distinguish "akathisia" as a separate syndrome from early, mild extrapyramidal symptomatology. For the control of extrapyramidal side effects, anti-parkinson drugs were administered with generally good results. The most frequently used anti-parkinson drug was Artane in doses of 2 to 5 mg. t.i.d. No patient in the present study was taken off fluphenazine because of side effects *per se* although the medication was stopped in some cases for other reasons. The extrapyramidal symptoms were investigated in terms of four variables: their relationship to dosage, sex, age, and clinical improvement.

Regarding the development of extrapyramidal side effects in relation to dosage, none were encountered at doses below five mg. per day. At five mg. per day and above, the neurological complications occurred at all dosage levels. In terms of over-all incidence, extrapyramidal side effects were as frequently seen below the mean dosage used as above. Thus, for the 22 patients on doses of 2-7.5 mg. per day, eight, or 26.7%, showed

the effects; while for the 19 patients on 9-20 mg. per day, five, or 20.8%, showed the effects. These figures refer to gross incidence and do not take into account the severity or form of the extrapyramidal side effects. It is our impression that the effects are less severe when they occur with lower dosages.

In terms of the incidence of the neurological complications according to sex, the incidence for female patients was 25.8% (8 out of 31 patients); for male patients, 21.7% (5 out of 23 patients). The higher incidence of these symptoms in female patients has been reported.[5]

The distribution of extrapyramidal side effects according to age revealed a very definite trend. The mean age for the 13 cases was 24.7 years, much younger than the over-all group mean of 36.9 years. Furthermore, the range of age for the patients developing extrapyramidal side effects was 19-35. Thus the entire group of 13 patients was confined to that segment of our treatment group 35 years or younger. The total number below 35 years was 23 patients, or 52.3%. The group above 35 years, comprising 21 patients, or 47.7%, was free of neurological complications. This finding was consistent for the sexes, the eight female patients developing extrapyramidal side effects having a mean age of 24.1 years while the five male patients had a mean of 25.8 years.

Our final consideration in the neurological complications was the relationship with clinical improvement. This is of considerable interest because of the theoretical implications of these side effects in behavioral response to phenothiazine.[5,6] In our limited series the appearance of extrapyramidal effects in the individual patient was not correlated with clinical improvement. Among the 13 patients developing extrapyramidal side effects, two became worse, six were unchanged, and five improved. This improvement rate of five out of 13 cases, or 38.5%, is considerably below that for the total group of 66.7%. Thus, while the presence of extrapyramidal side effects may be of importance in the spectrum of a drug's activity, the occurrence of the one effect is not necessarily related to clinical response.

"Side effects" in the placebo group included a range of subjective complaints. Of most interest were two patients who presented complaints quite similar to the subjective complaints usually associated with the mild dystonic extrapyramidal effects. The potency of a placebo was thus demonstrated in its "side effects" as well as its clinical effects.

Summary and Conclusions

Fluphenazine was administered to 54 patients within three days of their admission to a psychiatric receiving hospital. A placebo comparison group of 19 patients was also studied. With the patients in this series under the conditions of this study, fluphenazine appears to be of considerable usefulness. An over-all improvement rate of 66.7% was seen with fluphenazine in contrast to 36.8% with placebo.

The drug was administered two to three times a day for a total of 2 to 20 mg. per day. Generally, no better results were obtained with larger dosages (above 7.5 mg. per day) than with lower dosages. A dosage of 2 to 7.5 mg. per day appears most useful.

In terms of target symptom effects, despite the limited number of cases, fluphenazine showed definite usefulness for the depression and paranoia groups. Its effects on the anxiety group were no better than those of placebo.

The effects of fluphenazine on the target symptom of depression are of particular significance because of the specificity shown for schizophrenic depressions. The general impression to date with the current antidepressant drugs (the monoamine oxidase inhibitor group) has been that schizophrenic depressions are least benefited. The existence of a drug such as fluphenazine that may have particular use in this refractory group would be of real importance. In the present series the improvement of depression was seen in both male and female patients but in a higher proportion of male patients.

Side effects were benign and did not interfere with continued treatment. Extrapyramidal side effects were encountered in one-

quarter of the patients. These effects were not seen in dosages below five mg. per day, although progressively higher doses were not associated with an increasing incidence. The effects were readily controlled by anti-parkinson medication. No concurrence was seen between the presence of extrapyramidal side effects and clinical improvement.

Authors' Note: The foregoing study was undertaken by the Psychopharmacological Research Unit of the Downstate Medical Center, Brooklyn, N. Y., under the direction of David M. Engelhardt, M.D.

Fluphenazine is the generic name for 4-(3-[2-(trifluoromethyl)-10-phenothiazinyl] propyl)-1-piperazine ethanol dihydrochloride. For the present study it was supplied by E. R. Squibb & Sons as Prolixin.

REFERENCES

1. Himwich, H. E.: *Am. J. of Psychiat.*, 115:756-759, Feb. 1959.
2. Darling, H. F.: *Dis. of Nerv. Syst.*, 20:167-170, April 1959.
3. Taylor, I. J.: *Am. J. of Psychiat.*, 116:457-458, Nov. 1959.
4. The Squibb Institute for Medical Research, *E. R. Squibb & Sons*. Summary of Information for Clinical Investigators, Pi28, Prolixin, June 30, 1959.
5. Fink, M.: *International Congress of Psychiatry*, 2nd, Zurich, 1957.
6. Freyhan, F. A.: *Am. J. of Psychiat.*, 115:577-585, Jan. 1959.

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. et al.: *J.A.M.A. 160*:348 (Feb. 4) 1956.

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